

VOLUME 1

SURGICAL PATHOLOGY OF THE HEAD AND NECK

Third Edition

EDITED BY LEON BARNES



informa
healthcare

VISIT...

LANZAROTE
Caliente.COM

**SURGICAL
PATHOLOGY
OF THE
HEAD AND NECK**

VOLUME 1

**SURGICAL
PATHOLOGY
OF THE
HEAD AND NECK**
Third Edition

EDITED BY

LEON BARNES

*University of Pittsburgh Medical Center
Presbyterian-University Hospital
Pittsburgh, Pennsylvania, USA*

informa
healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

© 2009 by Informa Healthcare USA, Inc.
Informa Healthcare is an Informa business

No claim to original U.S. Government works
Printed in India by Replika Press Pvt. Ltd.
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-9163-8 (V1; Hardcover)
International Standard Book Number-13: 978-1-4200-9163-2 (V1; Hardcover)
International Standard Book Number-10: 1-4200-9164-6 (V2; Hardcover)
International Standard Book Number-13: 978-1-4200-9164-9 (V2; Hardcover)
International Standard Book Number-10: 1-4200-9165-4 (V3; Hardcover)
International Standard Book Number-13: 978-1-4200-9165-6 (V3; Hardcover)
International Standard Book Number-10: 0-8493-9023-0 (Set; Hardcover)
International Standard Book Number-13: 978-0-8493-9023-4 (Set; Hardcover)

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequence of their use.

No part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC) 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Library of Congress Cataloging-in-Publication Data

Surgical pathology of the head and neck / edited by Leon Barnes. – 3rd ed.
p. ; cm.

Includes bibliographical references and index.

ISBN-13: 978-0-8493-9023-4 (hb : alk. paper)

ISBN-10: 0-8493-9023-0 (hb : alk. paper)

1. Head–Diseases–Diagnosis. 2. Neck–Diseases–Diagnosis. 3. Pathology, Surgical. 4. Head–Tumors–Diagnosis.
5. Neck–Tumors–Diagnosis. I. Barnes, Leon, 1941–

[DNLM: 1. Head–pathology. 2. Neck–pathology. 3. Head–surgery. 4. Neck–surgery. 5. Pathology, Surgical.
WE 705 S961345 2008]

RC936.S87 2008

617.5'10754–dc22

2008026087

For Corporate Sales and Reprint Permissions call 212-520-2700 or write to:
Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

Visit the Informa Web site at
www.informa.com

and the Informa Healthcare Web site at
www.informahealthcare.com

Preface to Third Edition

Seven years have elapsed since the second edition of *Surgical Pathology of the Head and Neck* was published. During this interval there has been an enormous amount of new information that impacts on the daily practice of surgical pathology. Nowhere is this more evident than in the area of molecular biology and genetics. Data derived from this new discipline, once considered to be of research interest only, have revolutionized the evaluation of hematolymphoid neoplasms and are now being applied, to a lesser extent, to the assessment of mesenchymal and epithelial tumors. While immunohistochemistry has been available for almost 30 years, it has not remained static. New antibodies are constantly being developed that expand our diagnostic and prognostic capabilities.

Although these new technologies are exciting, they only supplement and do not replace the "H&E slide," which is, and will continue to be, the foundation of surgical pathology and this book particularly. This edition has been revised to incorporate some of these new technologies that further our understanding of the pathobiology of disease and improve our diagnostic acumen, while at the same time retaining clinical and pathological features that are not new but remain useful and important.

Due to constraints of time and the expanse of new knowledge, it is almost impossible for a single individual to produce a book that adequately covers the pathology of the head and neck. I have been fortunate, however, to secure the aid of several new outstanding collaborators to assist in this endeavor and wish to extend to them my sincere thanks and appreciation for lending their time and expertise. In addition to new contributors, the illustrations have also been changed from black and white to color to enhance clarity and emphasize important features.

This edition has also witnessed changes in the publishing industry. The two previous editions were published by Marcel Dekker, Inc., which was subsequently acquired by Informa Healthcare, the current publisher. At Informa Healthcare, I have had the pleasure of working with many talented individuals, including Geoffrey Greenwood, Sandra Beberman, Alyssa Fried, Vanessa Sanchez, Mary Araneo, Daniel Falatko, and Joseph Stubenrauch. I am especially indebted to them for their guidance and patience.

I also wish to acknowledge the contributions of my secretary, Mrs. Donna Bowen, and my summer student, Ms. Shayna Cornell, for secretarial support and Ms. Linda Shab and Mr. Thomas Bauer for my illustrations. Lastly, this book would not have been possible without the continued unwavering support of my family, Carol, Christy, and Lori, who have endured yet another edition!

Leon Barnes

Contents

Preface to Third Editioniii

Contributorsvii

Volume 1

- 1. Fine Needle Aspiration of the Head and Neck1**
Tarik M. Elsheikh, Harsharan K. Singh, Reda S. Saad, and Jan F. Silverman
- 2. Uses, Abuses, and Pitfalls of Frozen-Section Diagnoses of Diseases of the Head and Neck95**
Mario A. Luna
- 3. Diseases of the Larynx, Hypopharynx, and Trachea109**
Leon Barnes
- 4. Benign and Nonneoplastic Diseases of the Oral Cavity and Oropharynx201**
Robert A. Robinson and Steven D. Vincent
- 5. Noninfectious Vesiculoerosive and Ulcerative Lesions of the Oral Mucosa243**
Susan Müller
- 6. Premalignant Lesions of the Oral Cavity267**
Pieter J. Slootweg and Thijs A.W. Merckx
- 7. Cancer of the Oral Cavity and Oropharynx285**
Samir K. El-Mofty and James S. Lewis, Jr.
- 8. Diseases of the Nasal Cavity, Paranasal Sinuses, and Nasopharynx343**
Leon Barnes
- 9. Diseases of the External Ear, Middle Ear, and Temporal Bone423**
Bruce M. Wenig
- 10. Diseases of the Salivary Glands475**
John Wallace Eveson and Toshitaka Nagao

Volume 2

- 11. Midfacial Destructive Diseases649**
Leon Barnes
- 12. Tumors of the Nervous System669**
Beverly Y. Wang, David Zagzag, and Daisuke Nonaka
- 13. Tumors and Tumor-Like Lesions of the Soft Tissues773**
Julie C. Fanburg-Smith, Jerzy Lasota, Aaron Auerbach, Robert D. Foss, William B. Laskin, and Mark D. Murphey
- 14. Diseases of the Bones and Joints951**
Kristen A. Atkins and Stacey E. Mills

15. Hematolymphoid Lesions of the Head and Neck.....	997
<i>Alexander C. L. Chan and John K. C. Chan</i>	
16. Pathology of Neck Dissections	1135
<i>Mario A. Luna</i>	
17. The Occult Primary and Metastases to and from the Head and Neck.....	1147
<i>Mario A. Luna</i>	
18. Cysts and Cyst-like Lesions of the Oral Cavity, Jaws, and Neck	1163
<i>Steven D. Budnick and Leon Barnes</i>	
 Volume 3	
19. Odontogenic Tumors	1201
<i>Finn Prætorius</i>	
20. Maldevelopmental, Inflammatory, and Neoplastic Pathology in Children.....	1339
<i>Louis P. Dehner and Samir K. El-Mofty</i>	
21. Pathology of the Thyroid Gland	1385
<i>Lori A. Erickson and Ricardo V. Lloyd</i>	
22. Pathology of the Parathyroid Glands	1429
<i>Raja R. Seethala, Mohamed A. Virji, and Jennifer B. Ogilvie</i>	
23. Pathology of Selected Skin Lesions of the Head and Neck.....	1475
<i>Kim M. Hiatt, Shayestah Pashaei, and Bruce R. Smoller</i>	
24. Diseases of the Eye and Ocular Adnexa	1551
<i>Harry H. Brown</i>	
25. Infectious Diseases of the Head and Neck	1609
<i>Panna Mahadevia and Margaret Brandwein-Gensler</i>	
26. Miscellaneous Disorders of the Head and Neck	1717
<i>Leon Barnes</i>	
 <i>IndexI-1</i>	

Contributors

Kristen A. Atkins Department of Pathology, University of Virginia Health System, Charlottesville, Virginia, U.S.A.

Aaron Auerbach Department of Hematopathology, Armed Forces Institute of Pathology, Washington D.C., U.S.A.

Leon Barnes Department of Pathology, University of Pittsburgh Medical Center, Presbyterian-University Hospital, Pittsburgh, Pennsylvania, U.S.A.

Margaret Brandwein-Gensler Department of Pathology, Albert Einstein College of Medicine, Montefiore Medical Center—Moses Division, Bronx, New York, U.S.A.

Harry H. Brown Departments of Pathology and Ophthalmology, Harvey and Bernice Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.

Steven D. Budnick Emory University School of Medicine Atlanta, Georgia, U.S.A.

Alexander C. L. Chan Department of Pathology, Queen Elizabeth Hospital, Hong Kong

John K. C. Chan Department of Pathology, Queen Elizabeth Hospital, Hong Kong

Louis P. Dehner Lauren V. Ackerman Laboratory of Surgical Pathology, Barnes-Jewish and St. Louis Children's Hospitals, Washington University Medical Center, Department of Pathology and Immunology, St. Louis, Missouri, U.S.A.

Samir K. El-Mofty Department of Pathology and Immunology, Washington University, St. Louis, Missouri, U.S.A.

Samir K. El-Mofty Lauren V. Ackerman Laboratory of Surgical Pathology, Barnes-Jewish and St. Louis Children's Hospitals, Washington University Medical Center, Department of Pathology and Immunology, St. Louis, Missouri, U.S.A.

Tarik M. Elsheikh PA Labs, Ball Memorial Hospital, Muncie, Indiana, U.S.A.

Lori A. Erickson Mayo Clinic College of Medicine, Rochester, Minnesota, U.S.A.

John Wallace Eveson Department of Oral and Dental Science, Bristol Dental Hospital and School, Bristol, U.K.

Julie C. Fanburg-Smith Department of Orthopaedic and Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington D.C., U.S.A.

Robert D. Foss Department of Oral and Maxillofacial Pathology, Armed Forces Institute of Pathology, Washington D.C., U.S.A.

Kim M. Hiatt Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.

William B. Laskin Surgical Pathology, Northwestern Memorial Hospital, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, U.S.A.

Jerzy Lasota Department of Orthopaedic and Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington D.C., U.S.A.

James S. Lewis, Jr. Department of Pathology and Immunology, Washington University, St. Louis, Missouri, U.S.A.

Ricardo V. Lloyd Mayo Clinic College of Medicine, Rochester, Minnesota, U.S.A.

Mario A. Luna Department of Pathology, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

Susan Müller Department of Pathology and Laboratory Medicine and Department of Otolaryngology-Head & Neck Surgery, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

Panna Mahadevia Department of Pathology, Albert Einstein College of Medicine, Montefiore Medical Center—Moses Division, Bronx, New York, U.S.A.

Thijs A.W. Merckx Department of Oral and Maxillofacial Surgery, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Stacey E. Mills Department of Pathology, University of Virginia Health System, Charlottesville, Virginia, U.S.A.

Mark D. Murphey Department of Radiologic Pathology, Armed Forces Institute of Pathology, Washington D.C., U.S.A.

Toshitaka Nagao Department of Diagnostic Pathology, Tokyo Medical University, Tokyo, Japan

Daisuke Nonaka Department of Pathology, New York University School of Medicine, New York University Langone Medical Center, New York, New York, U.S.A.

Jennifer B. Ogilvie University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, U.S.A.

Shayesteh Pashaei Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.

Finn Prætorius Department of Oral Pathology, University of Copenhagen, Copenhagen, Denmark

Robert A. Robinson Department of Pathology, The University of Iowa, Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa, U.S.A.

Reda S. Saad Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada

Raja R. Seethala University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, U.S.A.

Jan F. Silverman Department of Pathology and Laboratory Medicine, Allegheny General Hospital, and Drexel University College of Medicine, Pittsburgh, Pennsylvania, U.S.A.

Harsharan K. Singh University of North Carolina-Chapel Hill School of Medicine, Chapel Hill, North Carolina, U.S.A.

Pieter J. Slootweg Department of Pathology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Bruce R. Smoller Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.

Steven D. Vincent Department of Oral Pathology, Oral Radiology and Oral Medicine, The University of Iowa College of Dentistry, Iowa City, Iowa, U.S.A.

Mohamed A. Virji University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, U.S.A.

Beverly Y. Wang Departments of Pathology and Otolaryngology, New York University School of Medicine, New York University Langone Medical Center, New York, New York, U.S.A.

Bruce M. Wenig Department of Pathology and Laboratory Medicine, Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York, New York, U.S.A.

David Zagzag Department of Neuropathology, New York University School of Medicine, Bellevue Hospital, New York, New York, U.S.A.

Fine Needle Aspiration of the Head and Neck

Tarik M. Elsheikh

PA Labs, Ball Memorial Hospital, Muncie, Indiana, U.S.A.

Harsharan K. Singh

University of North Carolina-Chapel Hill School of Medicine, Chapel Hill, North Carolina, U.S.A.

Reda S. Saad

Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada

Jan F. Silverman

*Department of Pathology and Laboratory Medicine, Allegheny General Hospital, and
Drexel University College of Medicine, Pittsburgh, Pennsylvania, U.S.A.*

I. THYROID GLAND

A. Introduction

Although clinically palpable thyroid nodules are only present in 4% to 7% of the adult population in the United States, the increasing use of diagnostic imaging has greatly increased the frequency of incidentally discovered thyroid nodules with a prevalence as high as 50% in many studies (1,2). These incidental thyroid nodules are usually detected with head and neck ultrasound (US) studies for carotid or parathyroid disease, and on computed tomography (CT), magnet resonance imaging (MRI), or positron emission tomography (PET) scans for the work-up of metastatic disease unrelated to the thyroid. However, the prevalence of cancer appears to be similar in palpable and nonpalpable thyroid nodules, ranging from 5% to 8%, with microinvasive papillary carcinomas being increasingly diagnosed at earlier stages because of widespread use of high-resolution US (1).

Fine needle aspiration (FNA) cytology has become the standard of care for the initial diagnostic workup of thyroid nodules. FNA of the thyroid gland is primarily a "screening test," but can be diagnostic in many conditions. Most clinicians use FNA results in conjunction with clinical findings to guide patient management. Clinical factors reported to be associated with increased risk of malignancy include head and neck irradiation, family history of medullary carcinoma or MEN2, extremes of age, male sex, a growing or fixed nodule, firm/hard consistency, cervical lymphadenopathy, and persistent hoarseness, dysphonia, dysphagia, or dyspnea (1). However, most patients with thyroid nodules have few or no symptoms, and usually no clear relationship exists between nodule histologic features or size and the reported symptoms. Clinicians generally use FNA to

provide a relative risk of malignancy from which they can base upon their management decisions, i.e., surgery versus clinical follow-up (3). FNA has achieved a 35 to 75% reduction in the number of patients requiring surgery, while doubling or tripling the incidence of malignancy detected at thyroidectomy (4). Therefore, the main priority of FNA is not to miss a cancer. Accordingly, high sensitivity coupled with a low false-negative rate is what most pathologists and clinicians stride towards achieving.

All patients with a palpable thyroid nodule should undergo US examination. Solitary palpable nodules may be sampled by freehand or US-guided FNA (US-FNA). In multinodular glands, sampling should be focused on lesions characterized by suspicious US features, rather than the larger or clinically dominant nodule (1). US-FNA is recommended for nonpalpable nodules larger than 1 cm (1). FNA is not recommended for nodules smaller than 1 cm, unless they demonstrate suspicious US features or the patient has a high-risk history.

Diagnostic Categories

In general, FNA results fall into one of four major diagnostic categories, with the relative frequency of diagnoses noted in parenthesis: benign (70%), indeterminate or suspicious (10–15%), malignant (5%), and nondiagnostic/unsatisfactory (10–15%) (5). The cytologic findings can be grouped into four to six categories, depending on whether or not the indeterminate category is further subdivided. We prefer to further subclassify the indeterminate category into three subgroups, as was recommended by the Papanicolaou Society of Cytopathology (PSC) in 2006 and National Cancer Institute (NCI) thyroid FNA state of the science conference in 2007 (Table 1) (6,7). The use of this terminology is presented later in the discussion of

Table 1 Thyroid Diagnostic Categories, as proposed by PSC and NCI State of the Science Conference

Category	Thyroid diagnosis
1	Benign, nonneoplastic
2	Follicular lesion of undetermined significance
3	Follicular neoplasm/Hurthle cell neoplasm
4	Suspicious for malignancy
5	Malignant
6	Unsatisfactory

Abbreviations: NCI, National Cancer Institute; PSC, Papanicolaou Society of Cytopathology

Source: Modified from Refs. 6, 7.

“follicular lesions.” The rendered cytologic diagnosis should be specific enough to help the clinician appropriately manage the thyroid condition. Increased communication between the clinician and the pathologist, and standardization of terminology within the pathology department will greatly improve patient care. Although the utilization of diagnostic categories is encouraged, they should not be used alone. These diagnostic categories need to be qualified with a specific diagnosis when possible, or with a differential diagnosis, in order to give the clinician the clearest idea possible of the likely risk of malignancy, i.e., a diagnosis of follicular lesion alone is not encouraged, but rather should be further qualified as hyperplastic nodule versus follicular neoplasm (FN) (8).

Diagnostic Accuracy

Sensitivity of thyroid FNA ranges from 65% to 98%, and specificity ranges from 72% to 100%. The false-positive rate varies from 0% to 7%, but is usually reported as below 1% if unsatisfactory, suspicious, and indeterminate diagnoses are excluded (3). The majority of false-positive diagnoses are due to overinterpretation of repair, hyperplastic papillae, and reactive nuclear changes as features of papillary carcinoma (3). False-negative rates range from 1% to 11%, and are predominately due to unsatisfactory/nondiagnostic specimens, sampling error, misinterpretation, and cystic neoplasms (especially cystic papillary thyroid carcinoma) (5,8).

Adequacy Criteria

The goal of FNA is to provide a specimen from which the pathologist can render an accurate and meaningful interpretation, which the clinicians can then use in their management of the patient. This implies a specimen with sufficient cellularity to yield a specific diagnosis that falls within one of the major diagnostic categories listed above (Table 1), i.e., benign/nonneoplastic, FN, malignancy. A diagnosis of “rare or few benign follicular cells” without qualification is, in our opinion, not considered an appropriate interpretation. An adequate sample should be representative of the lesion (appropriate cellularity) and technically well prepared, i.e., good fixation, thin smear, adequate staining. Unfortunately, judging specimen adequacy tends to be subjective and differs among pathologists.

As many as one-third of the cases initially diagnosed as “adequate and benign” were thought to be “nondiagnostic” on second review by other pathologists (9). Currently, there are no standardized criteria for judging aspirate sufficiency or cellularity. The most commonly cited adequacy criteria in the published literature are the presence of 5 to 6 groups of well preserved follicular cells with 10 or more cells per group (10); 10 or more clusters of follicular cells with more than 20 cells per cluster (11); 6 groups of follicular cells on at least 2 of 6 passes (12); and 8 to 10 clusters of follicular cells on each of two slides (13). With the application of these criteria, approximately 10% to 20% of thyroid aspirates fall in the nondiagnostic category. Repeat FNA, especially under US guidance, will result in an adequate specimen in about half of these cases (14). Despite repeat FNAs, however, 5% to 10% of patients will continue to have persistently nondiagnostic FNAs. Studies evaluating this subset of patients, with persistent nondiagnostic FNAs, have found an incidence of 2% to 37% of malignancy (14–16). Therefore, repeatedly nondiagnostic FNAs should be surgically excised (1).

The main purpose of establishing the adequacy criteria is to minimize the number of false-negative diagnoses. In our view, at least two passes are needed, as a single pass may not be representative. In our practice, we obtain at least three to four passes from each nodule to insure sampling of different areas. Exceptions include cystic lesions that collapse completely following aspiration (1). We employ a combined Kini-Hamburger criterion in our practice—at least six to eight groups of well-preserved follicular cells (10 or more cells per group) on at least each of two slides, preferably from two separate passes. We do not, however, restrict ourselves to these numbers when aspirates are predominately cystic or contain abundant colloid, as the presence of few benign follicular cells (3–4 groups) is sufficient to issue a diagnosis of benign/colloid nodule in these situations. However, in cystic change alone, i.e., macrophages without follicular cells, we generate a nondiagnostic interpretation, as up to 20% of cystic papillary carcinomas show only cystic change. Although abundant colloid alone represents a cytologically unsatisfactory specimen, we usually add a qualifier that colloid nodule is suggested if clinically benign, and recommend repeat US-FNA in six months. Using our criteria, follow-up thyroidectomy showed a 12% cancer rate in nondiagnostic specimens (17). This rate, however, may be slightly overestimated because of a selection bias, reflected by the fact that patients with clinically suspicious lesions are more likely to be referred for surgical excision. Individual centers should monitor their own diagnostic accuracy for guidance to their clinicians, and make it unambiguous when the specimen is unsatisfactory. Nondiagnostic FNAs should neither be considered benign nor be interpreted as “negative for malignancy.” Repeat FNA is encouraged, or excision may be indicated, especially in persistently nondiagnostic cases and high-risk patients (14). A specimen should not be interpreted as “unsatisfactory” in the presence of any degree of significant cytologic atypia, and should warrant an interpretation of “atypical” or “suspicious”.

Role of Repeat FNA in Thyroid

Indications for repeat FNA of thyroid nodules include follow-up of benign nodules, enlarging nodules, nodules larger than 4 cm, recurrent cyst, nonshrinkage of the nodule after levothyroxine therapy, and an initial unsatisfactory/nondiagnostic FNA (1). Repeat conventional (freehand) FNA in patients with initial unsatisfactory specimens results in an adequate sample in approximately 50% of cases (14). Conversely, repeat US-FNA of previously nondiagnostic biopsies can lead to a definitive diagnosis in up to 90% of cases and have resulted in a reduction in the unsatisfactory rate from 15% to 3% in some studies (18,19). This is especially helpful in small nodules less than 1.5 cm and complex cystic lesions, where needles can target the more solid component (4). Baloch et al. evaluated the role of repeat FNA in 50 unsatisfactory and "indeterminate for follicular neoplasm" cases, with surgical follow-up (20). Repeat US-FNA has led to a more definitive diagnosis in 80% of cases. Unsatisfactory diagnoses were associated with a 51% cancer rate, while "indeterminate" diagnoses were associated with a 48% cancer rate. Repeat FNA, however, is not recommended for "follicular neoplasm" diagnoses, as it creates confusion and does not provide additional useful management information (1). Repeat FNA should be performed at least three months following the initial FNA, to prevent post-FNA reparative changes (21). Flanagan et al. evaluated the role of repeat FNA in 267 patients with initial benign cytologic diagnoses, excluding unsatisfactory specimens, who had follow-up surgery (22). The use of one repeat FNA significantly increased the sensitivity for detecting malignancy from 82% to 90%, and decreased the false-negative rate from 17% to 11%. There was, however, no significant improvement in sensitivity or specificity when more than one repeat FNA were performed.

Normal Cytology and General Cytologic Features to Assess in Thyroid FNA

Generally, the presence of abundant colloid is associated with benign conditions, whereas scant to absent colloid is seen in neoplasms. Architecturally, a predominant honeycomb configuration of the thyroid cells and minimal microfollicle formation is associated with benign nonneoplastic conditions. Conversely, a predominant syncytial and/or microfollicular pattern is correlated with neoplasia. The normal thyroid cell nucleus is about the size of a red blood cell (RBC) (7–9 μ), and has finely granular chromatin, and small or inconspicuous nucleoli (Fig. 1). In nonneoplastic conditions, slight uniform enlargement and anisonucleosis can be observed. On the other hand, neoplasms may show considerable nuclear enlargement (3–4 times size of RBC), and variable pleomorphism.

B. Nonneoplastic Disease

Thyroiditis

Lymphocytic (Hashimoto's) thyroiditis. Lymphocytic thyroiditis is the most common type of thyroiditis encountered, and is characterized by variable numbers

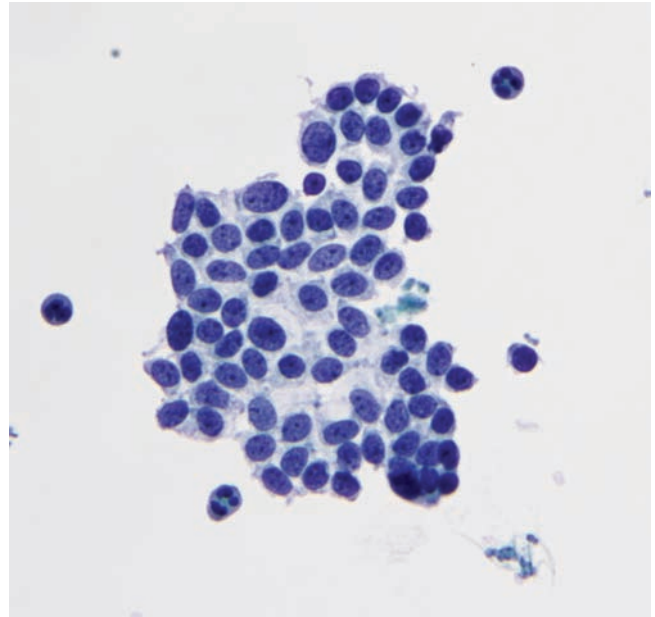


Figure 1 Normal thyroid follicular cells arranged in a honeycomb configuration. The nuclei have finely granular chromatin and small or inconspicuous nucleoli and show slight anisonucleosis (Papanicolaou stain; magnification, 600 $\times$).

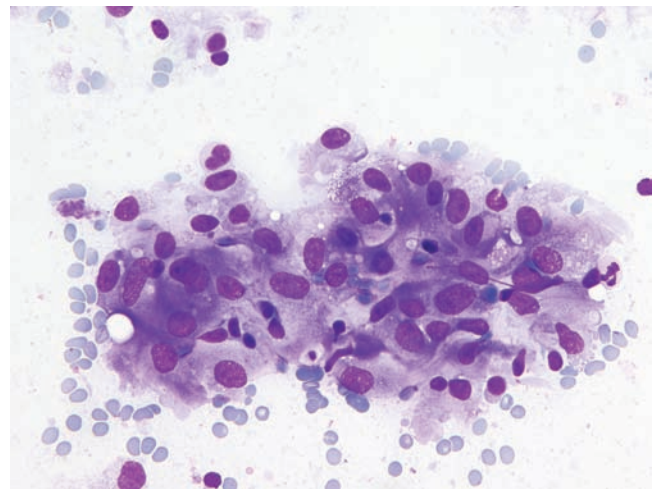


Figure 2 Hashimoto's thyroiditis. There is intimate admixture of oncocytes and lymphocytes (DQ stain; magnification, 400 $\times$).

of admixed lymphocytes and follicular cells (Fig. 2). Oncocytes may predominate in an aspirate, raising the differential diagnosis of oncocytic neoplasm. There is usually limited colloid, and the lymphoid population is polymorphic, showing admixture of small mature lymphocytes, larger reactive lymphoid cells, and occasional plasma cells. The inflammatory cells are often intimately admixed with the follicular cells. The differential diagnosis includes lymphoma, which is characterized by a monomorphic population of lymphoid cells. The follicular cells occasionally demonstrate reactive changes and

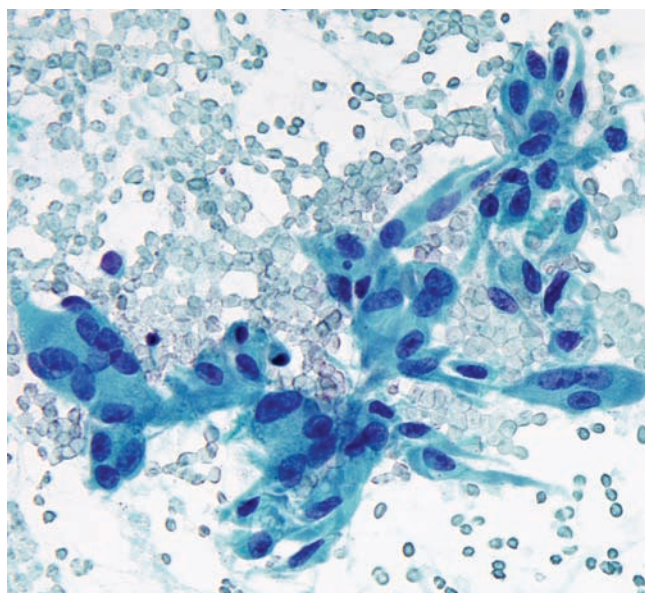


Figure 3 Hashimoto's thyroiditis associated with reactive changes, including nuclear enlargement and occasional nuclear grooves (Papanicolaou stain; magnification, 600 $\times$).

atypia, including nuclear grooves and nuclear enlargement (Fig. 3). Therefore, the diagnostic threshold for papillary thyroid carcinoma (PTC) should be raised in the presence of lymphocytic thyroiditis, and only considered when nuclear features of papillary carcinoma are diffusely present in a population of cells devoid of infiltrating lymphocytes (23). Nonspecific chronic inflammation may also be associated with nodular goiter.

The differential diagnosis of lymphocytic thyroiditis also includes thyroid lesions that may demonstrate lymphoepithelial features (Table 2). Thyroid tumors with thymus-like features are extremely rare and include a spectrum of tumors ranging from benign to malignant, such as ectopic thyroid thymoma and carcinoma showing thymus-like differentiation (CASTLE) (24). These tumors are identical in morphology to their mediastinal counterparts (25). CASTLE may demonstrate variable atypia ranging from bland morphology resembling thymoma, to highly atypical features resembling nasopharyngeal carcinoma, anaplastic carcinoma, or squamous carcinoma. The epithelial cells usually possess abundant eosinophilic/pale cytoplasm and large vesicular nuclei with

Table 2 Thyroid Lesions with Lympho-Epithelial Features

Lymphocytic thyroiditis
Lymphoma
Papillary thyroid carcinoma, i.e., Warthin-like and tall cell variants
Ectopic thymoma
Benign lymphoepithelial lesion
Carcinoma with thymus-like features
Metastatic carcinoma to intra or perithyroid lymph node
Neoplasm arising in a background of lymphocytic thyroiditis

prominent nucleoli and may be arranged in single cells and loosely cohesive groups (24,26). FNA of benign lymphoepithelial lesion is characterized by scant cellularity of the epithelial component and predominance of the lymphoid component. The squamous and mucinous epithelial component may show degenerative changes, but is devoid of significant atypia. PTC variants, such as Warthin-like, tall cell, and oncocytic types, arising in a background of lymphocytic thyroiditis should also be considered in the differential diagnosis (27). These tumors show oncocytic features including prominent nucleoli, granular cytoplasm, and admixed lymphocytes (20). The absence of nuclear features of PTC, however, excludes these entities from the differential diagnosis.

Subacute granulomatous (Dequervain's) thyroiditis. Subacute thyroiditis rarely presents for FNA, but with the presence of epithelioid granulomas, the cytologic features can be diagnostic. Nonspecific findings such as mixed inflammatory cells, proteinaceous debris, multinucleated giant cells, and scant degenerated follicular cells might be seen. The biopsy procedure, however, may be quite painful for the patient, preventing adequate sampling. In the late fibrotic stages of the disease, FNA is often nondiagnostic.

Acute thyroiditis. Acute thyroiditis is another cause of painful thyroid aspiration, and it is rarely sampled by FNA. The aspirates are rich in neutrophils, and are associated with scant reactive follicular cells, fibrin, macrophages, and blood. Bacteria or fungal organisms are occasionally seen in the background.

Nodular Goiter/Colloid Nodule

Nodular goiter or colloid nodule is the lesion most commonly sampled by FNA. Characteristically, there is abundant colloid and variable number of follicular cells (Fig. 4). Romanowsky/Diff-Quik[®] (DQ) stain best demonstrates the presence of colloid (especially watery

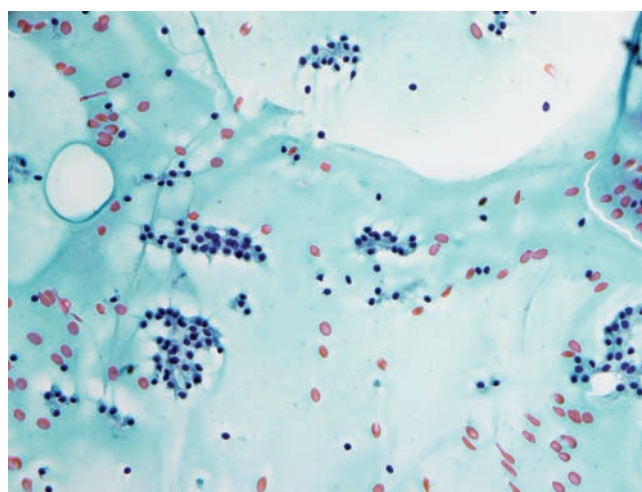


Figure 4 Colloid nodule showing abundant colloid and admixed benign thyroid follicular cells (Papanicolaou stain; magnification, 200 $\times$).

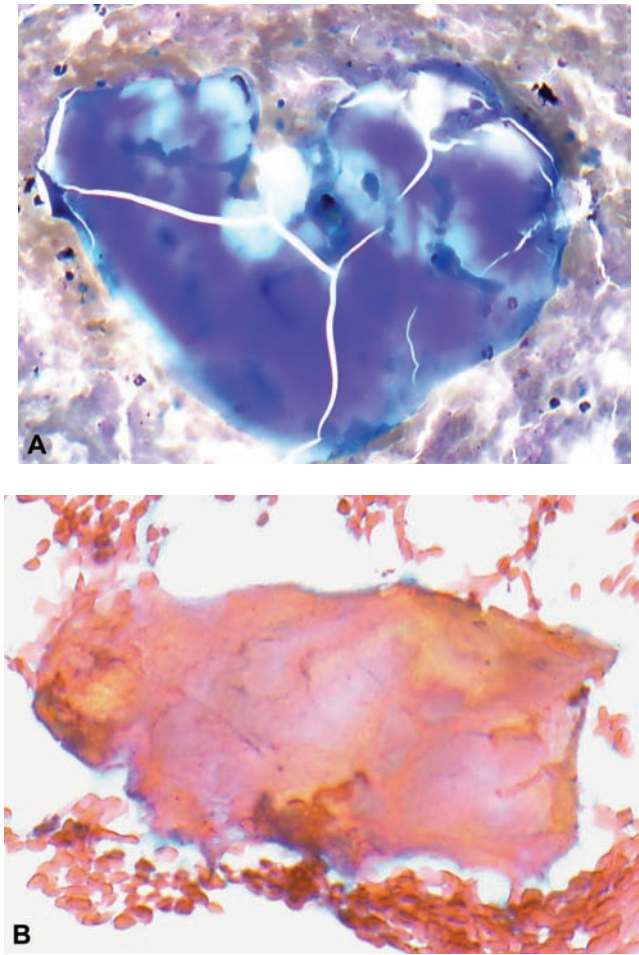


Figure 5 Dense colloid has a hyaline quality and stains blue-violet on air-dried smears (A) and dark orange on fixed preparations (B). Note prominent cracks [(A)DQ stain; magnification, 200× (B) Papanicolaou stain; magnification, 200×].

colloid). Colloid, when dense, is easy to recognize, has a hyaline quality, and often shows cracks. It has a dark blue-violet-magenta appearance on DQ stain, while stains dark green-orange with Papanicolaou (Fig. 5) (8). Thin watery colloid has a blue-violet appearance on DQ, and pale green-orange look on Papanicolaou stain (Figs. 4 and 6). It often forms a “thin membrane/cellophane” coating or film, frequently with folds imparting a “crazy pavement” appearance and/or cracks (Fig. 6) (8). Thin colloid, however, maybe difficult to recognize in Papanicolaou-stained specimens and may also disappear completely in thin-layer preparations (28). Thin colloid can also be confused with serum in bloody specimens. Helpful clues are the recognition of cracking and folding in colloid, as well as its tendency to surround follicular cells, whereas serum accumulates at the edges of the slide and around platelets, fibrin, and blood clots (3).

The individual thyroid follicular cells are small in size, arranged in monolayered sheets (Fig. 7) and/or large balls (Fig. 8), and show no significant nuclear overlapping or crowding. Occasional microfollicles can

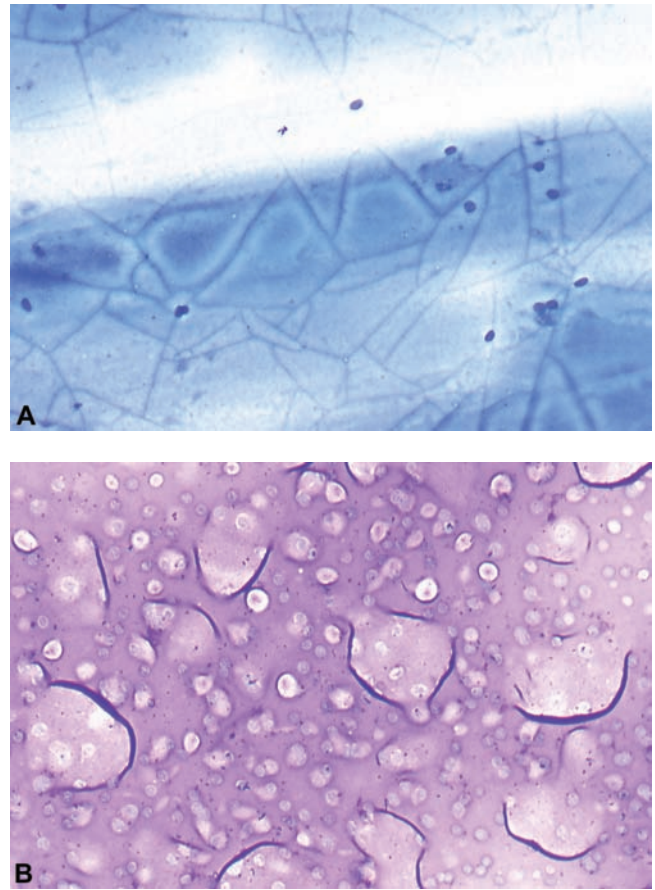


Figure 6 Thin watery colloid showing crazy pavement appearance (A) and cellophane-like coating with folds (B) (DQ stain, magnification, 200×).

be seen. The cytoplasm is delicate, scant, and may have small blue-black granules that are of no diagnostic significance, as they can be observed in benign and malignant conditions (29). Flat sheets of oncocyctic cells with mild anisonucleosis may be observed in some aspirates, but no significant atypia is demonstrated. The number of macrophages present in the background usually coincides with the extent of cystic degeneration. Many of the macrophages may contain hemosiderin pigment granules. Focal reparative changes might also be observed in cystic lesions, including the presence of spindle cells and cells with tissue culture medium appearance (30). Hyperplastic/adenomatoid nodules show increased cellularity compared to colloid nodules and may be confused with FNs. Detailed cytologic features of hyperplastic nodules are later discussed with follicular lesions.

Diffuse Goiter/Hyperthyroidism (Graves' Disease)

Most patients with Graves' disease have diffuse enlargement of the thyroid gland, and do not require biopsy. Occasionally, however, prominent nodules develop, that prompt FNA. The cytologic features of Graves' disease are nonspecific, and clinical correlation

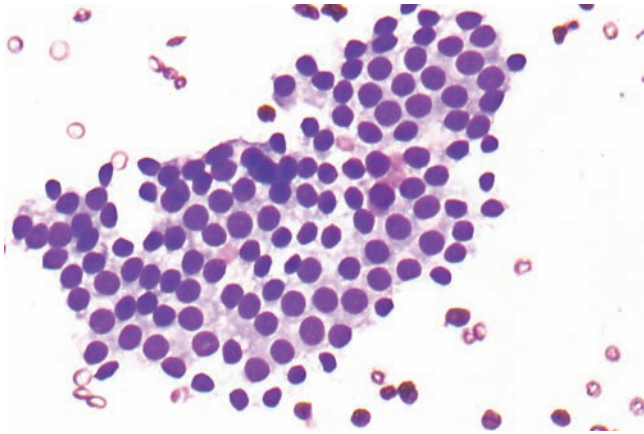


Figure 7 Colloid nodule. Flat sheets of benign thyroid cells with delicate cytoplasm and no significant nuclear overlapping (DQ stain; magnification, 400 $\times$).

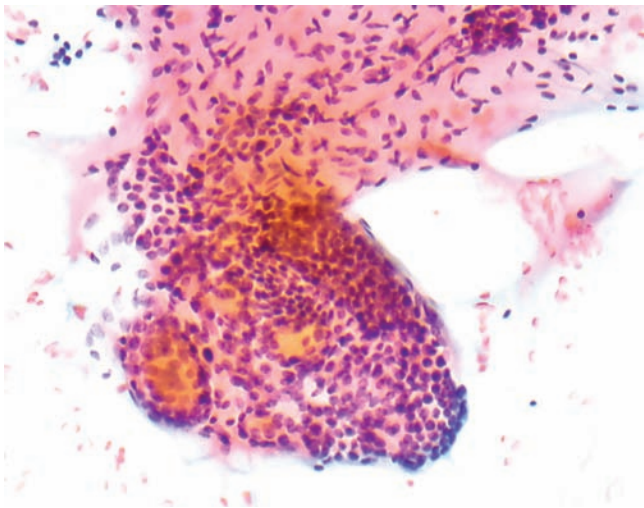


Figure 8 Colloid nodule. The follicular cells are arranged in large balls (microtissue fragments), but show no significant overlapping or atypia (Papanicolaou stain; magnification, 200 $\times$).

is needed for a definitive diagnosis. Specimens are often cellular, containing numerous follicular cells and thin colloid. Oncocytes and lymphocytes may be found in the background (3). The follicular cells are commonly arranged in flat sheets and have foamy delicate cytoplasm with distinctive flame cells. Flame cells are best appreciated on DQ stain and represent marginal cytoplasmic vacuoles with red to pink frayed edges (Fig. 9) (31). Flame cells, however, are not specific to Graves' disease as they may be encountered in other nonneoplastic thyroid conditions, FN, and papillary carcinoma. Occasionally, treated Graves' disease shows prominent microfollicular architecture, significant nuclear overlapping and crowding, and considerable atypia. Therefore, care must be taken to not

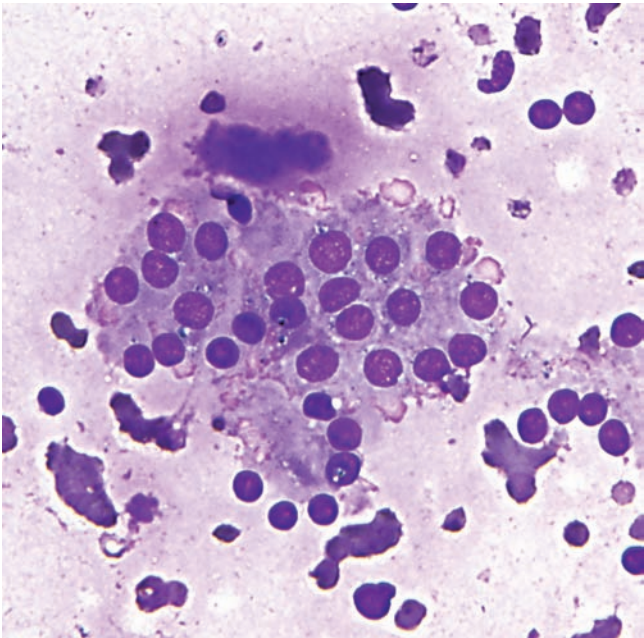


Figure 9 Hyperthyroidism (Graves' disease). The follicular cells are commonly arranged in flat sheets and have foamy delicate cytoplasm with distinctive flame cells. These flame cells, however, represent a nonspecific finding (DQ stain; magnification, 400 $\times$).

overdiagnose these changes as malignancy or neoplasia, and inquiry should be sought regarding prior radioactive iodine therapy (32). Sometimes the follicular cells display focal nuclear chromatin clearing, but other diagnostic nuclear features of papillary carcinoma such as grooves and inclusions are commonly absent (33).

C. Follicular Lesions

Follicular lesions of the thyroid represent the most problematic area in thyroid FNA cytology. The major entities included in the differential diagnosis comprise hyperplastic/adenomatoid nodule, FN (adenoma and carcinoma), and follicular variant of PTC (Table 3). Below is a discussion of the differential diagnosis of follicular lesions, cytologic criteria, terminology commonly used as well as terminology recently suggested by the PSC and NCI thyroid FNA state of the science conference, and the clinical implications of various diagnoses rendered (6,7). In general, smears containing abundant colloid are more likely to be benign, whereas markedly cellular aspirates are more likely to be neoplastic.

Table 3 Differential Diagnosis of Thyroid Follicular Lesions

Hyperplastic/adenomatoid nodule
Follicular Neoplasm
Follicular adenoma
Follicular carcinoma
Follicular variant of papillary carcinoma

Hyperplastic/Adenomatoid Nodule

Hyperplastic/adenomatoid nodule is characterized by the presence of abundant colloid and variable number of follicular cells. Often there is evidence of oncocyctic metaplasia and degenerative changes including macrophages and old blood. Hyperplastic nodule is considered in the differential diagnosis of FN when aspirates are cellular and contain scant colloid. Similar to colloid nodules, the follicular cells are arranged mainly in flat sheets with a honeycomb configuration (Fig. 7). A few microfollicular structures can be seen. Occasionally, balls and microtissue fragments are present (Fig. 8), especially when larger gauge needles are used. The nuclei are uniform in appearance and approximate the size of RBCs. They show finely granular chromatin with rare small nucleoli (Fig. 1). There is minimal nuclear overlapping and crowding.

FN (Adenoma and Carcinoma)

Using specific cytologic criteria, Kini et al. reported a 75% accuracy rate in the diagnosis of follicular carcinoma (34). Most other studies, however, could not reproduce such accuracy (35). In our opinion, and those of most expert cytopathologists, FNA cannot distinguish follicular adenoma from follicular carcinoma, since histologic confirmation is needed to demonstrate the presence of capsular and/or vascular space invasion. There are, however, several cytologic features reported to be associated with an increased cancer risk (40–60% cancer risk) (36). These features include an enlarged nuclei (at least twice the size of RBC), marked nuclear atypia including significant nuclear pleomorphism and irregularity, significant nuclear overlapping, and predominance of microfollicular structures (involving >75% of thyroid clusters) (36–40). Most follicular carcinomas (>90%) have prominent microfollicular architecture, while 10% to 15% of cases show significant cytologic atypia (41). It is important to emphasize, however, that the mere presence of microfollicles is not equated with neoplasia. In fact, studies have shown that microfollicles associated with no atypia had a low cancer risk comparable to that of benign FNA diagnoses (6% cancer risk) (36), and that microfollicles lacking nuclear overlap and mixed with abundant colloid had a 0% chance of harboring cancer (37). However, microfollicles with atypia were associated with a 44% cancer risk, while atypia with or without microfollicles was associated with malignancy in 60% of the cases, most of which represented follicular variant of papillary carcinoma (FVPC) (36).

FNAs of FN are typically highly cellular with scant colloid. There is prominent microfollicular and/or syncytial arrangement, involving greater than 50% to 75% of the cellular groups. Microfollicles are defined as groups of cells (6–12 cells) arranged in a ring or rosette-like configuration, and often display a repetitive pattern (Fig. 10) (41). The syncytial groups exhibit a three-dimensional appearance with loss of cell borders (Fig. 11). The nuclei are uniform and slightly enlarged, but usually demonstrate prominent overlapping and crowding. The chromatin is

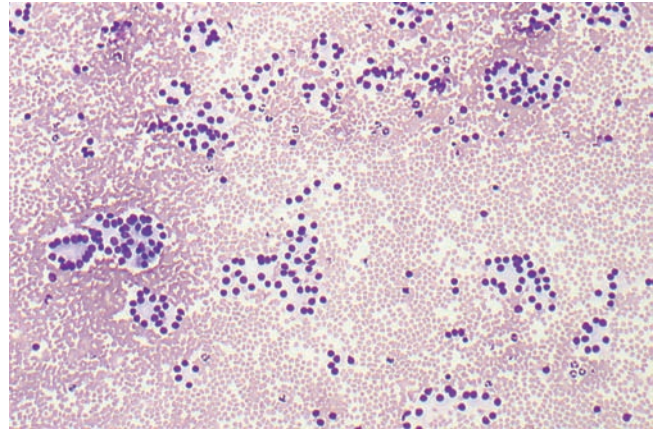


Figure 10 Follicular neoplasm showing prominent microfollicular architecture (DQ stain; magnification, 200×).

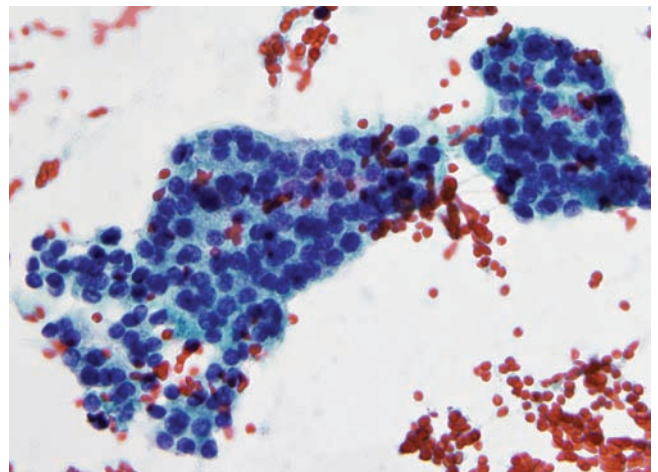


Figure 11 Follicular neoplasm showing syncytial groups of follicular cells. The cells have a uniform appearance and display prominent nuclear overlapping and crowding (Papanicolaou stain; magnification, 400×).

finely to coarsely granular, and nucleoli are infrequent (Fig. 11) (41). Significant nuclear atypia (which may or may not be present) is characterized by nuclear enlargement that is greater than twice the size of RBCs, coarse and clumped chromatin, and prominent enlarged nucleoli (Fig. 12). FVPC and medullary carcinoma should also be considered in the differential diagnosis.

Challenges in the Diagnosis of Hyperplastic/Adenomatoid Nodule and FN

Clearly, one of the most difficult problems in thyroid cytology is distinguishing hyperplastic nodule with little colloid from FN with some colloid (41). As

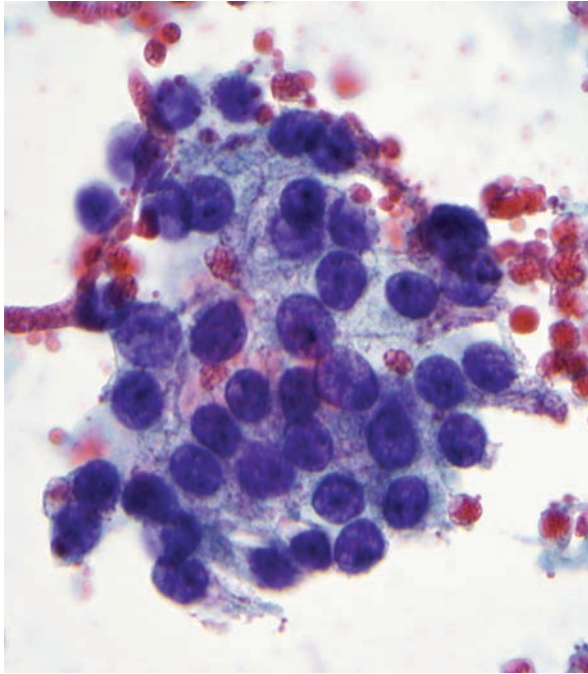


Figure 12 Follicular neoplasm with significant atypia, including nuclear enlargement, coarse and clumped chromatin, and prominent nucleoli (Papanicolaou stain; magnification, 600 $\times$).

previously mentioned, the mere presence of microfollicles is not diagnostic of FN, as microfollicles may be focally seen in 5% to 10% of hyperplastic nodules. Up to 30% of hyperplastic nodules are highly cellular, and 15% to 20% show scant colloid (42,43). Although degenerative changes are often associated with hyperplastic nodule, they may be found in up to 30% of FN. A definitive diagnosis of hyperplastic nodule should not be made in the absence of colloid (3,41–43). Low cellularity may be encountered in aspirates of FN because of poor biopsy techniques or because of a macrofollicular architecture yielding abundant colloid and scant follicular cells. Some FNs are highly vascular, yielding abundant blood, and rare follicular groups with prominent nuclear overlapping and/or microfollicular architecture (44). Oncocytic change and flame cells may also be found in FN (benign and malignant), in addition to hyperplastic nodule and colloid nodule.

Several studies have evaluated the variability in reporting and diagnosing FN and cellular hyperplastic nodules (40,45,46). The areas of greatest debate and confusion included terminology and criteria employed in diagnosing FN. Differences in terminology involved mainly the use of two diagnostic categories (i.e., follicular lesion and FN) versus one category. Some pathologists apply the terms follicular lesion and FN interchangeably, while others require more stringent criteria for the diagnosis of FN. Other than increased cellularity, the criteria used by cytopathologists in the diagnosis of FN vary from strict to none. For example, the proportion of microfollicles needed to establish a

FN diagnosis has ranged in the literature from none to predominant. There was no clear definition of how cellular an aspirate needed to be in order to be classified as “hypercellular.” There were also major disagreements in recognizing colloid, especially when it had a watery-thin appearance or was associated with considerable blood in the background (46). A wide range of interobserver variability (fair to substantial) has been reported, even among pathologists from the same institution, when cases diagnosed as follicular lesion and FN were examined (45). Clary et al. reported a higher accuracy in predicting neoplastic (84% sensitivity) over nonneoplastic (66% specificity), which supported the utility of FNA as more of a screening test in these conditions (45). Other studies analyzed clinical factors that may complement FNA in predicting malignancy, including size more than 4 cm, fixed lesions, younger patients, male sex, solitary nodule, etc. Clinical history, however, is provided to the pathologist in only up to one-third of the cases (45).

Follicular Lesions, Grey Zone, and Terminology

Although the terms “follicular lesion” and “follicular neoplasm” are used interchangeably by some authors, we do not consider them synonymous. According to literature review, lesions categorized as indeterminate account for 5% to 42% of FNA diagnoses. We do not recommend the use of “indeterminate” as a stand-alone diagnosis, as its meaning has not been standardized and may be interpreted in different ways. Indeterminate has been used by different authors and institutions to refer to a variety of diagnoses, including FN, follicular lesion, suspicious for malignancy, and atypia not otherwise specified. Redman et al. surveyed 133 clinicians (endocrinologists, surgeons, and thyroid specialists) in order to determine the implications of FNA diagnoses on management options (47). In this study, clinicians appropriately opted for repeat FNA in 98% of the nondiagnostic cytologic terminology, and elicited a 96% surgical excision response to “suspicious” diagnoses. However, clinicians chose repeat FNA (58%) or surgery (32%) for indeterminate diagnoses, and selected repeat FNA (37%) or surgery (52%) for “atypical” designations (47). The study clearly demonstrated that confusion arose with the atypical and indeterminate diagnoses. Indeterminate was confused with nondiagnostic in some cases, while atypical was too ambiguous and treated as suspicious in many other cases. The majority of clinicians, on the other hand, correctly interpreted the nondiagnostic and suspicious diagnoses. The indeterminate category, in reality, includes two types of lesions with different clinical implications: (i) truly indeterminate, showing features intermediate between hyperplastic/colloid nodule and FN which may be best managed by repeat FNA, clinical follow-up, and correlation with US and ancillary studies; and (ii) follicular patterned lesion consistent with FN, in which repeat biopsy is unlikely to clarify the situation, and surgery would be indicated (8).

Two European studies found no malignancy on follow-up of FNAs diagnosed as follicular lesion and FN (48,49). The authors advocated a less aggressive

approach to management, i.e., clinical follow-up. The authors, however, did not apply strict criteria, and FN was loosely defined as hypercellular smears associated with scant colloid and microfollicles, with no mention of the percentage of microfollicle formation, nuclear atypia, or other architectural patterns. Architectural features and nuclear atypia, in addition to colloid and cellularity, should be evaluated in these hypercellular specimens, so pathologists can better define and classify those gray-zone lesions and lessen the number of cases classified as indeterminate. We recommend subdividing the indeterminate category, as was recommended by the PSC and NCI, into (i) Follicular lesion of undetermined significance (FLUS) and (ii) FN (6,7).

Follicular Lesion of Undetermined Significance

In 2006, the PSC introduced the terminology “cellular lesion cannot rule out FN,” addressing lesions falling in the gray zone (6). In 2007, The NCI thyroid state-of-the-science conference suggested similar terminologies, including “FLUS,” “a typical follicular lesion,” and “atypia of undetermined significance” (7). These terminologies were chosen in order to avoid the confusing terms of “follicular lesion,” “indeterminate,” “atypical,” etc. as stand alone diagnoses. This designation of “FLUS” is employed when the major differential diagnosis is between hyperplastic nodule and FN. These aspirates are often highly cellular and have scant colloid. There is admixture of flat sheets and microfollicles/syncytial fragments, with minimal nuclear overlapping and crowding (Fig. 13A). This diagnosis is also rendered when smears from different passes show mixed cytologic findings ranging from “benign” to “possible FN.” Bloody specimens of low cellularity, but containing microfollicles and prominent nuclear overlap (highly vascular lesions) would also be included in this category (Fig. 13 B). This latter cytologic clue, although important in recognizing some FN, has rarely been emphasized in the literature (40).

D. Oncocytic (Hurthle Cell) Neoplasms

Similar to FN, the separation of oncocytic adenoma from carcinoma requires histologic evaluation for evidence of capsular and/or vascular space invasion. Oncocytic neoplasms usually render highly cellular aspirates with scant colloid and rare to absent lymphocytes. The oncocytes are arranged mainly in large and small clusters and isolated single cells (Fig. 14). Occasional microfollicles may be seen. The cells show uniform appearance, and have abundant granular cytoplasm with well-defined borders, round to oval nuclei, granular chromatin, and prominent nucleoli. Cytologic atypia may be observed in oncocytic lesions, including scattered nuclear enlargement and pleomorphism (50). A variety of other neoplastic and nonneoplastic lesions may show oncocytic/granular features (Table 4). The main differential diagnosis includes oncocytic nodule in association with a nodular goiter or lymphocytic thyroiditis. Admixture of benign thyroid follicular cells and colloid favors nodular goiter, while a prominent

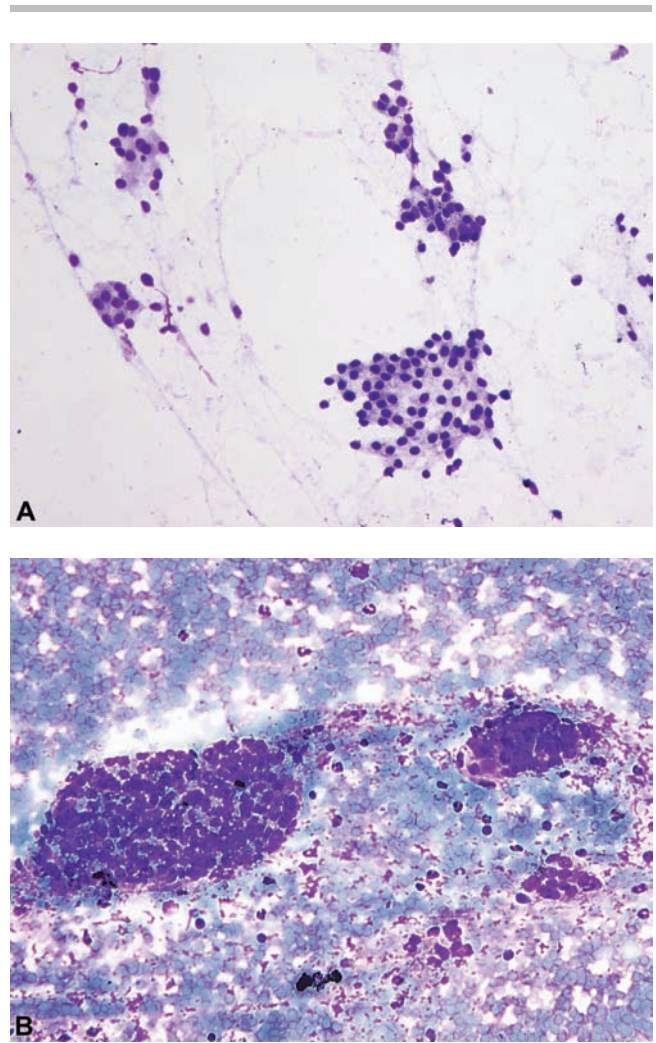


Figure 13 Follicular lesion of undetermined significance (A) This specimen showed admixture of flat sheets and microfollicles, with no significant atypia, and scant to absent colloid. (B) This bloody aspirate had rare clusters of follicular cells with prominent nuclear overlapping, and occasional microfollicles [(A) DQ stain; magnification, 400× (B) DQ stain; magnification, 200×].

lymphoid cell component favors lymphocytic thyroiditis. Endocrine neoplasms such as medullary carcinoma, paraganglioma, and parathyroid adenoma may show considerable variability in cell size and shape, including polygonal to spindle cells with ill-defined granular cytoplasm and frayed borders. In medullary carcinoma, the nuclei typically have a “salt and pepper” chromatin, but may show pleomorphism with prominent nucleoli, and scattered stripped atypical nuclei. The cytologic features of metastatic renal cell carcinoma (RCC) are discussed later in the chapter.

E. Malignant Neoplasms

Papillary Thyroid Carcinoma

PTC is the most commonly encountered thyroid malignancy. It can be partially cystic, or entirely cystic

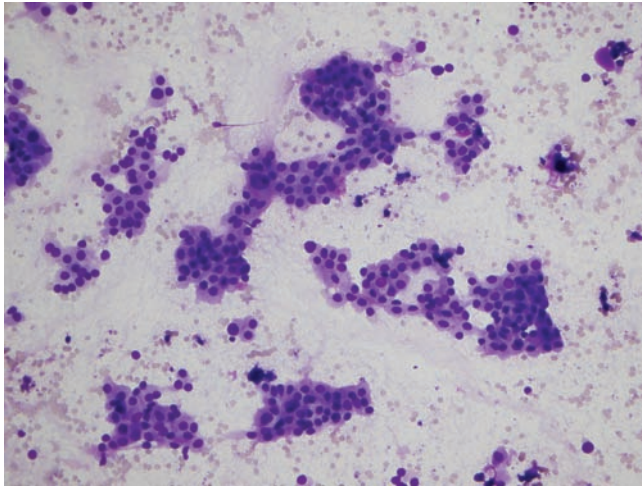


Figure 14 Oncocytic (Hurthle cell) neoplasm showing sheets of oncocytic cells and minimal to absent colloid (DQ stain; magnification, 200 $\times$).

Table 4 Thyroid Lesions with Oncocytic (Hurthle)/Granular Cell Features

Oncocytic neoplasm
Lymphocytic thyroiditis
Nodular goiter
Medullary carcinoma
Papillary carcinoma: oncocytic, tall cell, and Warthin-like variants
Parathyroid adenoma
Paraganglioma
Metastatic renal cell carcinoma

in up to 10% of cases. Classic PTC shows distinctive architectural and cytologic features. Architectural features include the presence of papillary and tightly cohesive three-dimensional clusters of neoplastic cells (Fig. 15). Many of the neoplastic groups demonstrate prominent nuclear crowding and overlapping. Thick colloid with a “bubble-gum” appearance may be present in the background in up to one quarter of the cases (Fig. 16) (42). In most cases, the cytoplasm has a thick “metaplastic” consistency, with well-defined borders (51). Occasionally, especially in cystic PTC, the neoplastic cells show prominent cytoplasmic microvacuolization resembling macrophages (52). The hallmark for diagnosing PTC, however, is based on its distinctive nuclear features. The diffuse presence of nuclear grooves, nuclear enlargement, and finely granular (powdery) chromatin must be present, before a definitive diagnosis is rendered (Fig. 17). The ground glass appearance of the nuclei seen in histologic sections is an artifact of formalin fixation and is not recognized in cytologic preparations. Nuclear grooves may traverse the entire longitudinal axis of the nucleus, or may appear as invaginations of the nuclear membrane. Intranuclear pseudoinclusions, which are also distinctive of PTC, are not present in

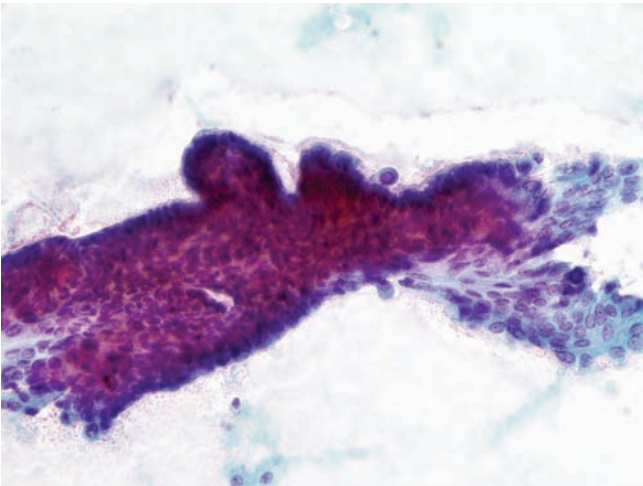


Figure 15 Papillary carcinoma, classic type. Tightly cohesive clusters with papillary architecture are seen (Papanicolaou stain; magnification, 400 $\times$).

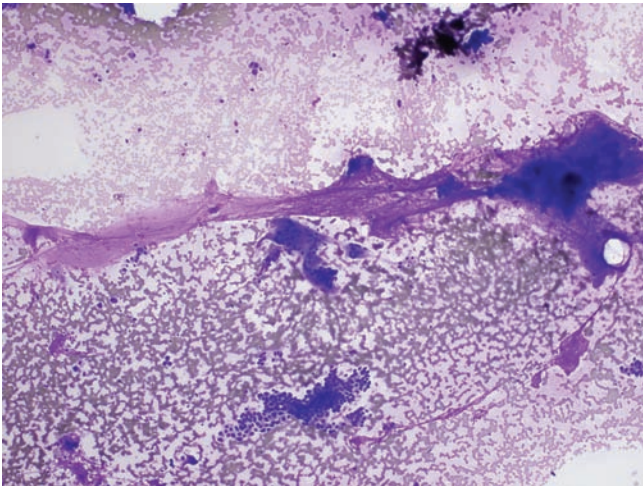


Figure 16 Papillary carcinoma showing thick colloid with a “bubble-gum” appearance in the background (DQ stain; magnification, 200 $\times$).

all cases. These inclusions usually have sharp margins, and should reflect the color of the cytoplasm of that cell (not just a clear hole in the nucleus) (53). Nucleoli are often small and peripherally situated against a thickened nuclear membrane. The presence of psammoma bodies, although not diagnostic by itself, should raise a red flag for PTC, and may be seen in up to 40% of cases (13). A proportion of cases show multinucleated giant cells, the presence of which should increase awareness about the possibility of PTC, and invoke a more thorough search for diagnostic nuclear features (Fig. 18). It is important to note that there is no single feature that is diagnostic of PTC,

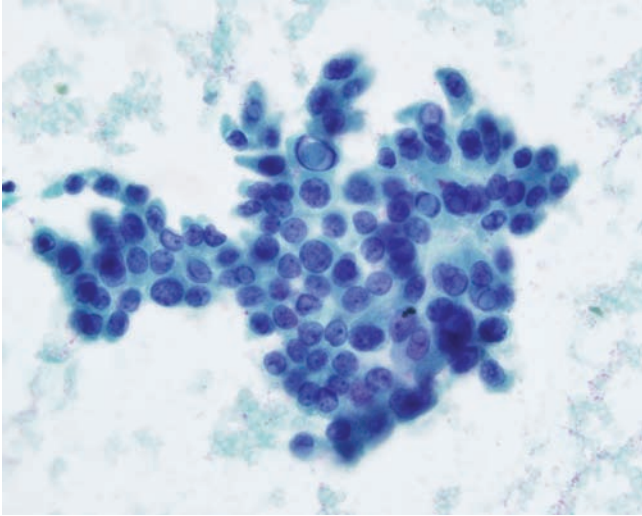


Figure 17 Papillary carcinoma demonstrating characteristic nuclear features, including powdery chromatin, grooves, and intranuclear pseudoinclusions (Papanicolaou stain; magnification, 600 $\times$).

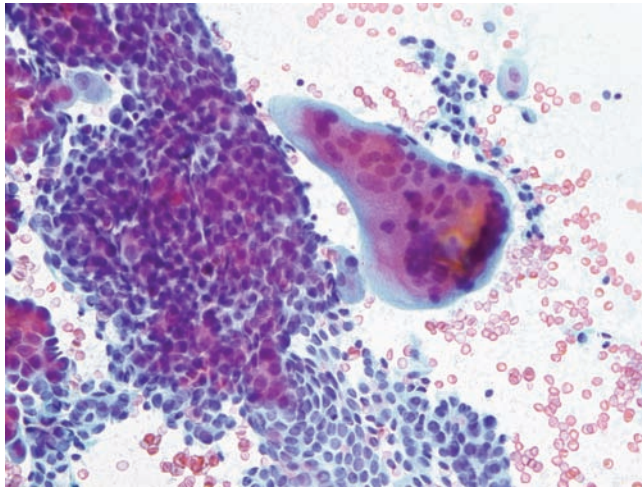


Figure 18 Multinucleated giant cells associated with papillary carcinoma (Papanicolaou stain; magnification, 400 $\times$).

and that a definitive diagnosis should be based on a constellation of cytologic features. Several studies have attempted to determine the most sensitive cytologic criteria for diagnosing classic PTC, and found nuclear inclusions, nuclear grooves, papillary structures, and metaplastic cytoplasm, when present in combination, to be the most reliable cytologic features (13,42,51,54). PTC may show prominent cystic change, and this accounts for PTC being the most common cystic neoplasm of the thyroid (55). FNA is unable to establish a diagnosis of malignancy, however, in 50%

of entirely cystic PTC (56). This is mainly due to scant cellularity and prominent degenerative changes. The aspirate may consist predominately of foamy macrophages, blood, and reparative changes. Other neoplastic and nonneoplastic lesions may also be associated with prominent cystic change (discussed later in the section on cystic lesions). When nuclear features of PTC are diffusely present in the neoplastic cells, a specific diagnosis can be rendered, but, occasionally, PTC nuclear features are only found focally. However, the presence of nuclear grooves and nuclear inclusions in association with fine powdery chromatin, even focally, should always raise a warning flag, and elicit a “suspicious for PTC” diagnosis.

Variants of Papillary Thyroid Carcinoma

There are several described variants of PTC, including follicular, tall cell, oncocytic, and columnar cell. Follicular variant of PTC (FVPC) is by far the most common of these subtypes. By definition, no papillary structures are identified, and the neoplasm consists predominately of follicular structures. The aspirates mainly display branching monolayered sheets, which are considered to be a significant low-power discriminating feature from other follicular-patterned neoplasms (Fig. 19) (57). The combination of flat syncytial sheets, nuclear enlargement, and fine powdery chromatin, were found to be the most sensitive criteria, whereas the combination of nuclear enlargement, fine chromatin, and nuclear grooves were the most specific, in establishing the diagnosis of FVPC (Fig. 20) (58). Intranuclear pseudoinclusions are seen in less than half the cases. Fulciniti et al. also emphasized the presence of nuclear grooves and nucleoli over intranuclear inclusions in the diagnosis of FVPC (57). The importance of both architectural and nuclear features in establishing the diagnosis of FVPC cannot

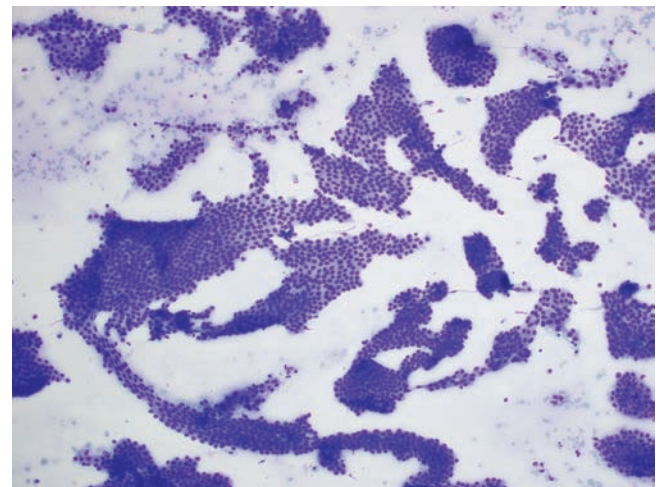


Figure 19 Follicular variant of papillary carcinoma showing a distinctive low power appearance of branching monolayered sheets (DQ stain; magnification, 200 $\times$).

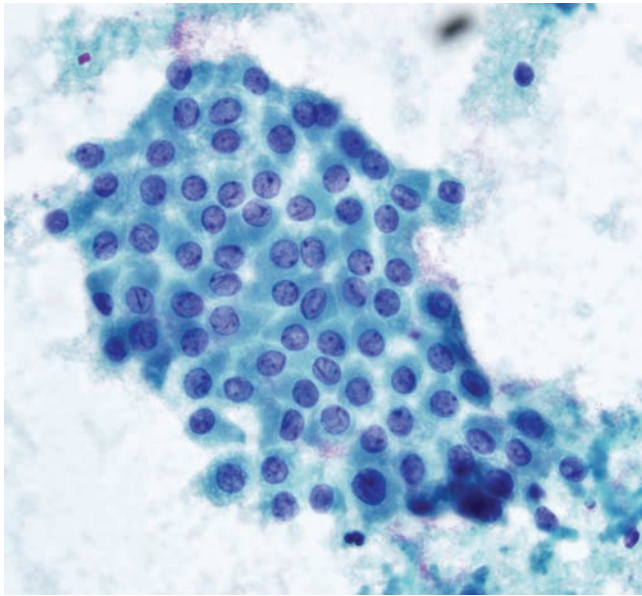


Figure 20 Follicular variant of papillary carcinoma. The combination of nuclear enlargement, fine chromatin, and nuclear grooves were found to be most specific in establishing the diagnosis. Softer criteria include nuclear membrane thickening and eccentric placement of nucleoli against the nuclear membrane (Papanicolaou stain; magnification, 600 $\times$).

be overstressed. The predominance of microfollicles in some cases can lead to misclassification as FN, and a predominant monolayered sheet pattern may be misinterpreted as honeycomb sheets associated with nodular goiter. However, careful high-power examination of the nuclei and recognition of the nuclear features of PTC in these cases will usually establish the diagnosis of FVPC, and prevent those potential pitfalls. Not infrequently, FVPC may show abundant colloid or paucity of nuclear features of PTC, leading to a misdiagnosis of benign thyroid disease or FN. In fact, FVPC is only second to sampling error as the most common cause of false-negative diagnoses in thyroid FNA. Wu et al. reported 11 false-negative cases of FVPC, where 6 cases were attributed to sampling error (micropapillary carcinoma), and 5 cases showed focal atypia in a background of abundant colloid and cystic change (17).

The *oncocytic (Hurthle cell) variant of PTC* is characterized by large tumor cells with abundant dense cytoplasm, well-defined cytoplasmic borders, eccentric nuclei, and nuclear features of PTC (Fig. 21). The *tall cell variant of PTC* shows elongated tumor cells with enlarged nuclei, overlapping and stratification of nuclei, and dense eosinophilic cytoplasm (Fig. 22). The nuclear features of PTC, in tall cell variant, are often diffuse and extensive, compared with classic PTC. The *columnar cell variant of PTC* demonstrates elongated to columnar cells with ill-defined cell borders, delicate cytoplasm with focal vacuolization/clearing, nuclear pseudostratification, and oval to elongated hyperchromatic nuclei (59). Architecturally, it may resemble

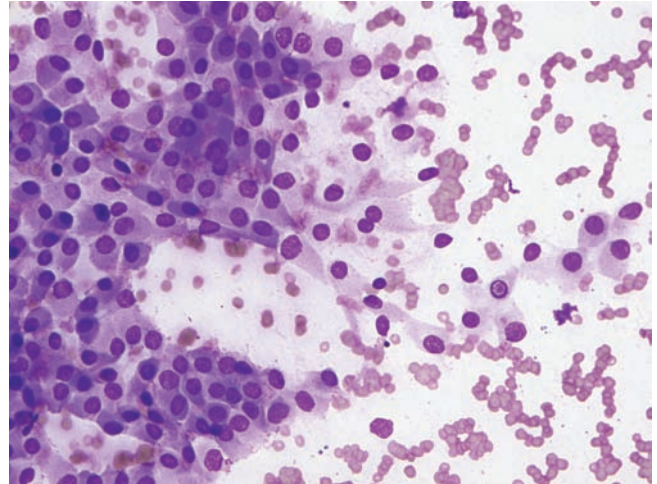


Figure 21 Oncocytic (Hurthle cell) variant of papillary carcinoma. The neoplastic cells show cytoplasmic oncocytic features, but demonstrate nuclear features of papillary carcinoma, including a rare intranuclear inclusion (at 4:00) (DQ stain; magnification, 400 $\times$).

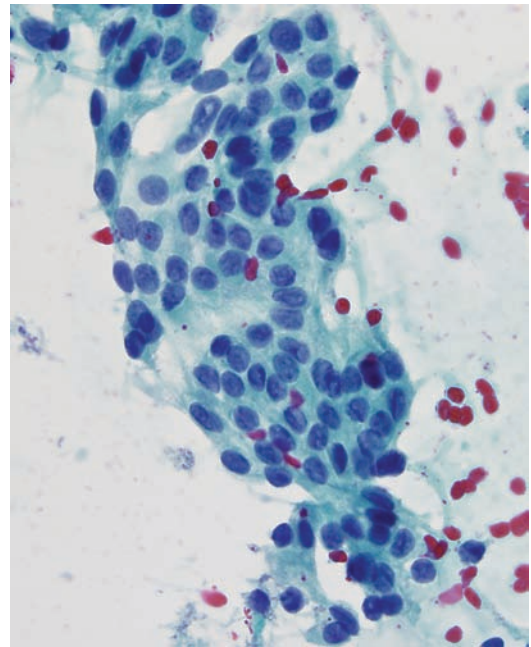


Figure 22 Tall cell variant of papillary carcinoma. Elongated tumor cells with abundant cytoplasm, enlarged overlapping nuclei, and characteristic nuclear features of papillary carcinoma (Papanicolaou stain; magnification, 600 $\times$).

colonic adenocarcinoma. Cytologic classification of PTC is accurate in over 90% of classic PTC, and in most FVPC, but is much less reproducible in other PTC variants (59). Tall cell and oncocytic variants of PTC, in particular, show significant overlap in their

cytologic appearance. It is more important, in our opinion, to be familiar with the spectrum of cytologic appearances of PTC than it is to render a specific PTC-variant diagnosis.

Suspicious for PTC

We issue a diagnosis of suspicious for PTC when nuclear features of PTC are only focally present. These nuclear features, however, must be present in combination (Fig. 23), and include rare nuclear grooves, nuclear enlargement, and powdery chromatin. Focal nuclear grooves and/or intranuclear inclusions (by themselves) can be found in a variety of other neoplastic and nonneoplastic conditions, including nodular hyperplasia, lymphocytic thyroiditis, FN, and medullary carcinoma (3). It is important to recognize “suspicious for PTC” as a distinct category, and not to lump it with other indeterminate or FN diagnoses, because of its substantially greater association with malignancy on surgical follow-up. Logani et al. and Wu et al. reported cancer follow-up rates of 77% and 75%, respectively, when rendering such diagnoses (60). This is in contrast to the cancer follow-up rate of 10% to 30% typically associated with indeterminate or FN diagnoses. With such an increased risk of malignancy, clinicians and patients may consider total thyroidectomy as an alternative option to lobectomy. Another management choice includes lobectomy with intraoperative consultation, which has been shown to be helpful in an additional 30% of cases (23).

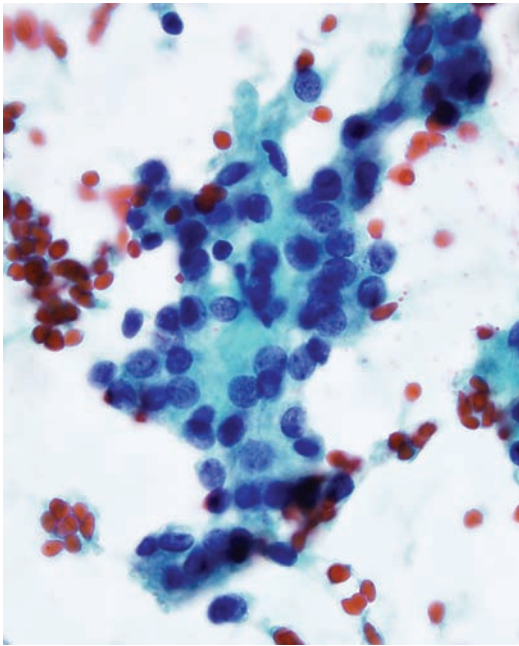


Figure 23 Suspicious for papillary carcinoma. This case showed nuclear enlargement, powdery chromatin, rare nuclear grooves, and no nuclear pseudoinclusions (Papanicolaou stain; magnification, 600 $\times$).

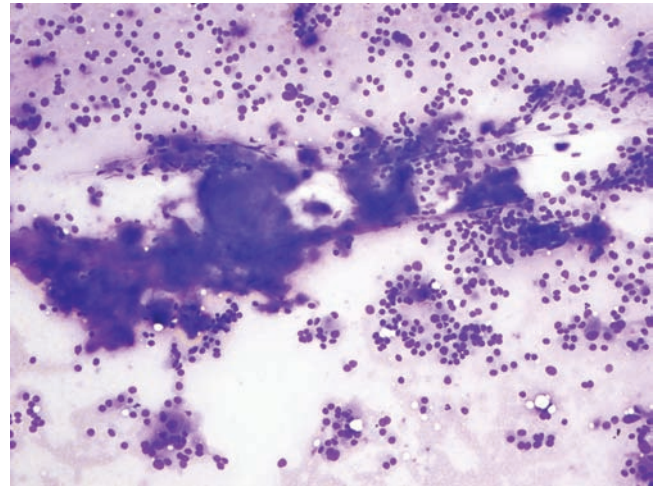


Figure 24 Medullary carcinoma. There are many single cells, as well as clusters with a microacinar configuration (carcinoid-like appearance). Amyloid is present in the background (DQ stain; magnification, 200 $\times$).

Medullary Carcinoma

Medullary carcinoma is notorious for its variable cytologic appearances, ranging from a monomorphic to a pleomorphic cell population. Typically, medullary carcinoma presents mostly as isolated cells with occasional clusters (Fig. 24). The neoplastic cells may have a plasmacytoid, spindle, epithelioid, or carcinoid-like appearance, but often a mixture of different cell types is encountered in the same specimen (Figs. 24–26). The cytoplasm has a delicate lacy quality, and may show

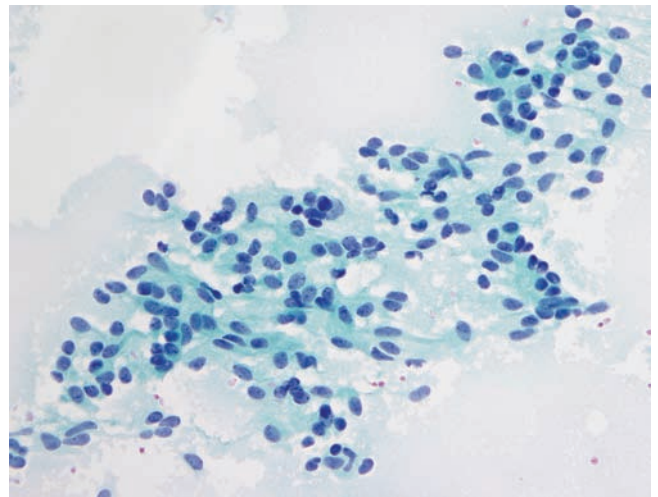


Figure 25 Medullary carcinoma showing variable appearance, including loosely cohesive groups of uniform cells with delicate cytoplasm, round to oval nuclei, and occasional spindling. The nuclei have a salt and pepper chromatin pattern (Papanicolaou stain; magnification, 400 $\times$).

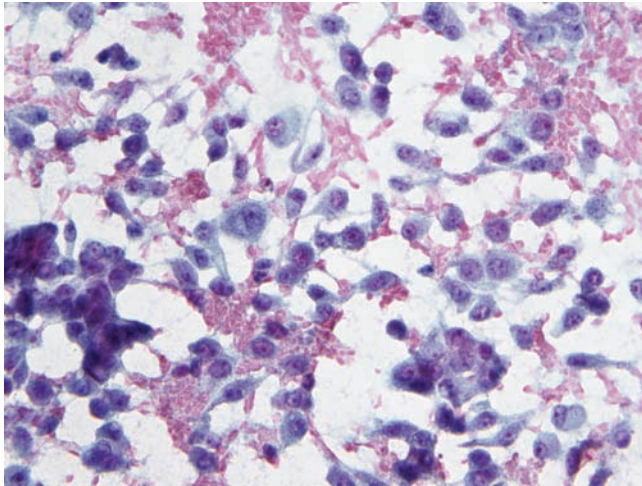


Figure 26 Medullary carcinoma consisting predominately of single cells with abundant cytoplasm and eccentric nuclei (plasmacytoid appearance). There is also significant nuclear pleomorphism and prominent nucleoli (Papanicolaou stain; magnification, 600 $\times$).

pink cytoplasmic granules. Sometimes, the neoplastic cells show a predominately oncocytic appearance, mimicking oncocytic neoplasms (Fig. 27). However, oncocytic neoplasm usually has cells with well-defined borders, in contrast to ill-defined wispy borders of medullary carcinoma. Clear cell change may be observed, but is often only focally present. The nuclei are round to oval, with finely to coarsely granular chromatin (salt and pepper), and have small or inconspicuous nucleoli (Fig. 25). Binucleation and multinucleation are common. Occasional intranuclear inclusions are appreciated in some cases (Fig. 27) (61). Variable amount of amyloid may be present in the

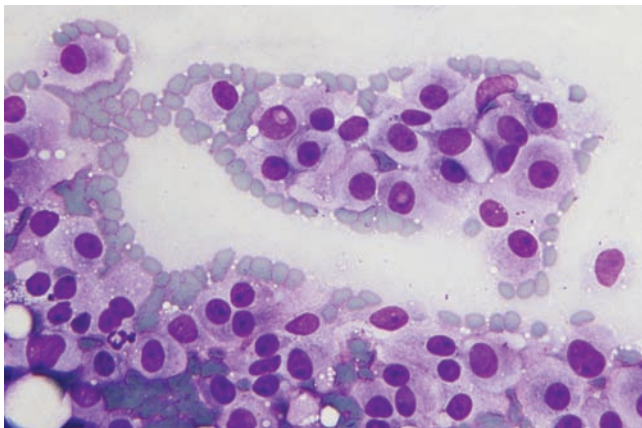


Figure 27 Medullary carcinoma with a predominant oncocytic appearance. Notice scattered intranuclear inclusions (DQ stain; magnification, 600 $\times$).

background (Fig. 24). Amyloid has an appearance similar to thick colloid, but is confirmed with Congo red stain. Immunocytochemical stains for calcitonin and neuroendocrine markers such as chromogranin and synaptophysin are extremely helpful in establishing the diagnosis. The tumor cells are usually positive for carcinoembryonic antigen (CEA), but negative for thyroglobulin. Serum calcitonin levels are elevated in most patients, and help establish the diagnosis. The differential diagnosis includes oncocytic neoplasm, papillary carcinoma, plasmacytoma, and mesenchymal tumors. Oncocytic tumors show prominent nucleoli and lack the neuroendocrine chromatin pattern. Although medullary carcinoma may display intranuclear holes, it will not show other diagnostic nuclear features of PTC such as nuclear grooves and powdery chromatin (62). In addition, PTC is negative for calcitonin and chromogranin, and is positive for thyroglobulin. Mesenchymal tumors and spindle cell melanoma are included in the differential diagnosis of predominantly spindle medullary carcinoma, while plasmacytoma and melanoma may be confused with plasmacytoid medullary carcinoma. Immunohistochemistry (IHC) can play a pivotal role in establishing a definitive diagnosis in those cases.

Insular Carcinoma/Poorly Differentiated Carcinoma

Insular carcinoma is a rare aggressive malignancy characterized histologically by the presence of focal or diffuse insular pattern. FNA smears are usually highly cellular and composed of monomorphic appearing small follicular cells, occurring singly and in clusters (63). Occasionally, intact insulae of follicular cells surrounded by hyaline stroma are seen. The neoplastic cells show scant delicate cytoplasm with round hyperchromatic nuclei, coarsely granular chromatin, and mild-to-moderate nuclear irregularities. Many naked nuclei are often present in the background. Microfollicles as well as infrequent grooves and inclusions can be seen, mimicking FN and PTC. In our experience, and those of others, a definitive diagnosis of insular carcinoma cannot be established by FNA (63). Most cases are diagnosed as FN or suspicious for malignancy. A helpful clue as to the aggressive nature of this tumor is the presence of increased mitotic activity and individual cell necrosis.

Anaplastic Carcinoma

Anaplastic carcinoma is the most aggressive of all primary thyroid cancers and is usually unresectable or present with metastatic disease. Therefore, an accurate FNA diagnosis may spare the patient unnecessary surgery, in favor of radiation therapy (3). Cytologically, anaplastic carcinoma presents as isolated cells and loose groups. The malignant cells show extreme nuclear pleomorphism and atypia, and may have a spindle, giant cell, or small cell appearance (Fig. 28). Occasional multinucleated forms are seen. Typically, the nuclei have coarsely irregular chromatin and prominent macronucleoli. Differential diagnosis includes poorly differentiated components of papillary, follicular, and medullary carcinoma. Anaplastic

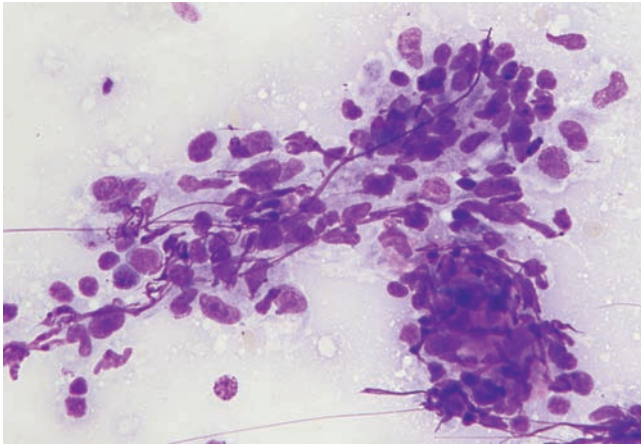


Figure 28 Anaplastic carcinoma. There are loosely cohesive groups of extremely pleomorphic cells with spindle cell appearance (DQ stain; magnification, 600×).

carcinoma, therefore, can only be considered in the absence of well-differentiated components. Cytokeratin stain may be employed to exclude sarcoma, lymphoma, and melanoma. In contrast to FNs, PTC, and medullary carcinoma, anaplastic carcinoma is infrequently positive for thyroid transcription factor-1 (TTF-1). The differential diagnosis also includes granulation tissue, repair, I^{131} therapy effect, and metastatic carcinoma. Abundant necrosis may be present in the background, rendering an unsatisfactory diagnosis. Therefore, the presence of rare pleomorphic cells associated with necrosis in an elderly patient should raise the possibility of anaplastic carcinoma and trigger additional studies.

Lymphoma

FNA cytology of thyroid lymphoma is similar to its lymph node counterpart. Most patients have an already established history of lymphoma. Non-Hodgkin's lymphoma (NHL) is by far the most common type, with Hodgkin's disease representing a rarity in the thyroid. Diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone B-cell lymphoma are the most common types. The smears have a monomorphic lymphoid appearance and show many lymphoglandular bodies in the background. Flow cytometry and/or immunocytochemistry are necessary for establishing a definitive diagnosis, particularly in patients with no previous history. Differential diagnosis includes lymphoid hyperplasia and lymphocytic thyroiditis (Table 5), both of which are characterized by a polymorphic population of lymphoid cells. Flow cytometry is often required to separate low-grade lymphoma from lymphoid hyperplasia. CD45, CD20, CD3, calcitonin, chromogranin, CEA, and cytokeratin may be needed in difficult cases, to distinguish lymphoma from medullary carcinoma and small cell carcinoma.

Table 5 Differential Diagnosis of Lymphoid Lesions of Thyroid

Lymphocytic thyroiditis
Lymphoid hyperplasia in peri- or intrathyroid lymph node
Lymphoma
Medullary carcinoma
Small cell carcinoma

Suspicious for Malignancy

We use this diagnostic category when the cytologic features are suggestive of a specific malignancy, but a definitive diagnosis cannot be rendered. A definitive diagnosis of malignancy may not be rendered due to quantitative reasons (i.e., malignant appearing cells, but limited cellularity) or qualitative reasons (i.e., focal or less than well developed features of malignancy). The most commonly encountered example of this diagnostic category is "suspicious for PTC" (Fig. 23). It is imperative to establish "suspicious for malignancy" as a distinct and separate diagnostic category and not to combine it with indeterminate or FN diagnoses because of its significantly increased association with malignancy on follow-up surgery. "Suspicious for PTC" has a reported cancer follow-up rate of approximately 75% (58,60). With such a high risk of malignancy, clinicians and patients may consider total thyroidectomy as an alternative management option to lobectomy. Intraoperative consultation may also be suggested. Careful attention to cytologic details is especially needed when examining cystic lesions, as atypical reparative changes in benign cysts may be confused with malignancy (41).

F. Cystic Lesions

Thyroid cysts account for approximately 15% to 25 % of all thyroid nodules, and are most commonly due to cystic degeneration in nodular goiter. Thyroid cyst fluid may be clear yellow, hemorrhagic, or dark brown. It usually contains macrophages (Fig. 29), inflammatory cells, colloid, and degenerated follicular cells. Features associated with benign cysts include complete drainage of the cyst with no residual mass, no recurrence, and absence of cytologic atypia. Lining cells from benign cysts often show reparative features, including flat sheets of evenly spaced cells with elongated shape, dense cytoplasm, distinct cell borders, and prominent nucleoli. The major differential diagnostic consideration in these cases is cystic PTC vs. benign cyst. Studies have shown that 7% to 29% of thyroid cysts are malignant (64). Cystic PTC often lacks the repair-like spindle morphology and shows atypia characterized by papillary architecture, nuclear enlargement and crowding, nuclear grooves, and rare intranuclear inclusions (64). Atypical features may also be focally encountered in benign cysts and include rare cells with nuclear grooves and fine pale chromatin, which could raise the suspicion for PTC (Fig. 30). Other atypical features associated with cystic change such as fibroblastic proliferation and atypical repair, including atypical elongated round or bizarre cells, can be confused with malignancy (41). Some

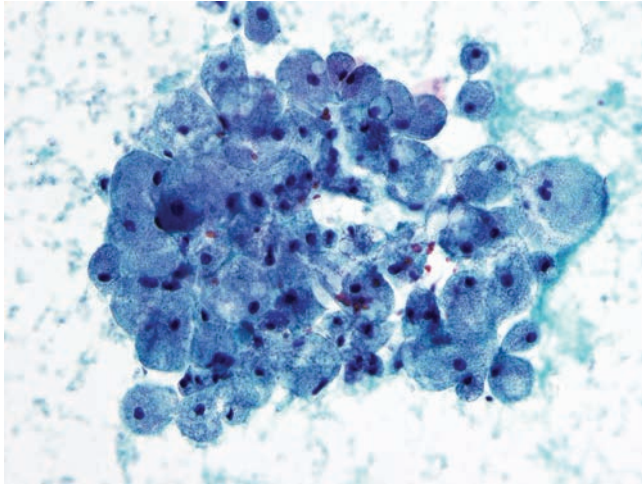


Figure 29 Macrophages associated with cyst, showing vacuolated cytoplasm, small uniform nuclei and small nucleoli (Papanicolaou stain; magnification, 600×).

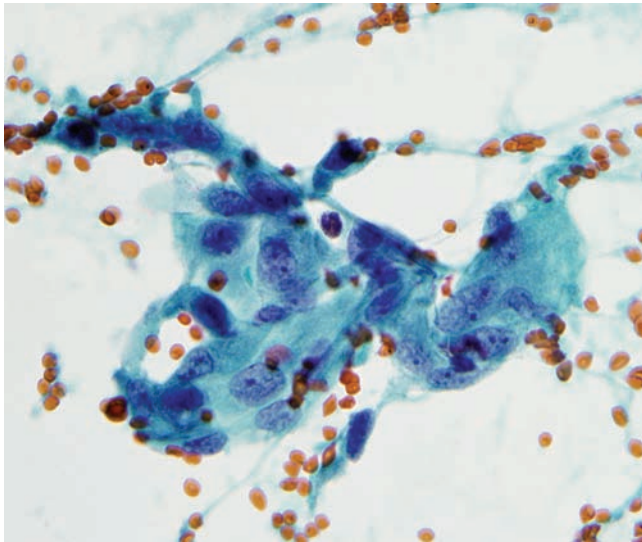


Figure 30 Reparative and reactive cellular changes associated with benign cyst. Note fine pale chromatin, occasional nuclear groove, spindling, and prominent nucleoli (Papanicolaou stain; magnification, 600×).

aspirates show rare atypical cells with a hobnail or histiocytoid appearance, enlarged nuclei, granular chromatin, and abundant vacuolated cytoplasm, but lack nuclear grooves and intranuclear inclusions (Fig. 31). Although seldom encountered in aspirates, these atypical histiocytoid cells have been strongly associated with PTC, and should provoke an atypical diagnosis when observed (65). It is important to be aware of these atypical cells as they can be easily dismissed and misclassified as macrophages. Any residual mass

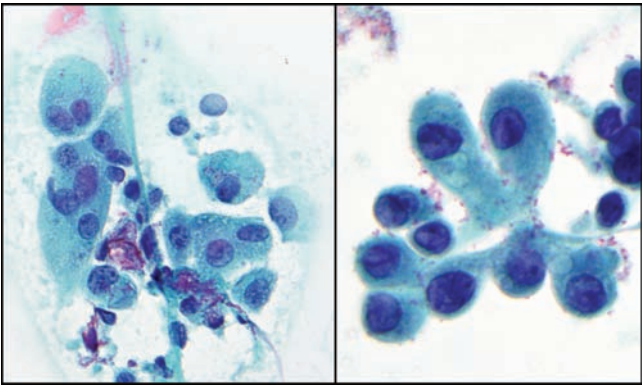


Figure 31 Atypical histiocytoid cells showing abundant vacuolated cytoplasm, enlarged nuclei, granular chromatin, and prominent nucleoli. These cells have been strongly associated with papillary carcinoma (Papanicolaou stain; magnification, 400×).

Table 6 Differential Diagnosis of Thyroid Cysts

Nodular goiter/colloid nodule
Simple cyst
Lymphocytic thyroiditis
Thyroglossal duct and Branchial cleft cyst
Parathyroid cyst
Follicular and oncocytic neoplasm
Malignant neoplasms, especially papillary carcinoma

remaining after aspiration of a cyst should be sampled. FNA, however, remains unable to establish a definitive diagnosis in approximately 50% of cystic malignancies. Therefore, patients should undergo careful follow-up, with possible repeat FNA under US guidance in three to six months. Other entities included in the differential diagnosis of cystic lesions are listed in Table 6. Generally, the gross appearance of the aspirated cyst fluid is a poor indicator of the nature of the cyst. Clear-colorless fluid, however, should suggest a parathyroid cyst, and trigger submitting cyst fluid for parathyroid hormone measurements (66). Thyroglossal duct cyst is congenital and is located in the midline of the neck, superior to the thyroid gland. It occasionally, however, lies inferior to the hyoid bone and gets confused with the thyroid gland. Cytologic specimens are of low cellularity and contain degenerated squamous and/or columnar epithelial cells admixed with macrophages and proteinaceous material. Thyroid tissue is found in approximately 50% of cases.

G. Clear Cell Lesions

Cellular proliferations with clear cell features raise the possibility of primary and secondary thyroid neoplasms (Table 7). Metastatic Renal Cell Carcinoma (RCC) should first be excluded, when a neoplasm displays prominent clear cell change. Detailed clinical history is crucial. FNA of RCC shows single cells and

Table 7 Thyroid Tumors with Clear Cell Features

Metastatic renal cell carcinoma
Follicular adenoma
Follicular carcinoma
Papillary carcinoma, i.e., columnar cell variant
Medullary carcinoma
Paraganglioma
Parathyroid adenoma
Histiocytes and cyst lining cells
Salivary gland type cancers, i.e., mucoepidermoid carcinoma
Other metastatic cancers, i.e., lung, head and neck, breast, liver, germ cell tumor

sheets with moderate to abundant finely vacuolated/clear cytoplasm and frayed cytoplasmic borders (Fig. 32). Nuclear to cytoplasmic ratios may range from low to high, and nucleoli may or may not be prominent. Occasionally, vascularized epithelial fragments are seen. FN (adenoma or carcinoma) may show clear cell features; however, these changes are usually focal, and there is often an associated prominent microfollicular architecture and/or syncytial arrangement, and pronounced nuclear overlap and crowding. Columnar cell variant of PTC shows clear cytoplasm, but architecturally resembles colonic carcinoma, i.e., pseudostratification and elongated cells with hyperchromatic nuclei (63). Primary mucoepidermoid carcinoma (MEC) is rarely reported in the thyroid, but shows focal clear cell change and cytologic features similar to those described in the salivary glands, including an admixture of metaplastic type squamous cells, mucin producing cells and intermediate cells (67). Clustering of histiocytes and cyst lining cells may at times raise the possibility of neoplasia (Figs. 29 and 30); however, these aspirates are of scant cellularity and show spindling and degenerative changes. Finally, other metastatic cancers from such sites as lung, head

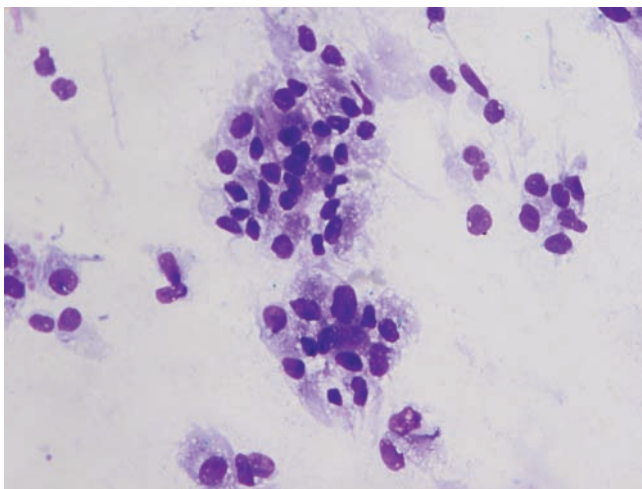


Figure 32 Metastatic renal cell carcinoma. FNA shows clusters and single cells with abundant finely vacuolated cytoplasm and frayed cytoplasmic borders. There is mild nuclear atypia (DQ stain; magnification, 400 $\times$).

and neck, breast and liver, as well as germ cell tumors, may show prominent clear cell features and should be considered in the differential diagnosis.

H. Metastatic Malignancies to the Thyroid

The thyroid gland is a rare site for involvement by metastatic malignancy, with a reported incidence of 1.3 to 25 % (68). Metastasis to the thyroid can present as multiple small nodules, or as a solitary tumor mass mimicking a primary neoplasm (Table 8) (69). In some cases, metastasis to the thyroid can become manifest long after the detection of primary cancer; this scenario is especially encountered with RCC (68). Breast and lung cancers are the most common primary tumors seen in autopsy studies, while the kidney is the most common site reported in surgical series (70). Melanoma and colon cancers not infrequently metastasize to the thyroid (Fig. 33). The thyroid may also be involved by direct extension from carcinomas of the upper aerodigestive tract, such as squamous carcinoma and adenoid cystic carcinoma (ACC). Metastasis should be suspected when the microscopic features appear alien to those neoplasms more commonly encountered in the thyroid such as PTC, FN, and medullary carcinoma. Michelow and Leiman reported

Table 8 Malignancies Metastatic to the Thyroid Gland

Kidney
Lung
Breast
Colon
Melanoma
Direct extension from upper aerodigestive tract, i.e., squamous carcinoma, adenoid cystic carcinoma (ACC)

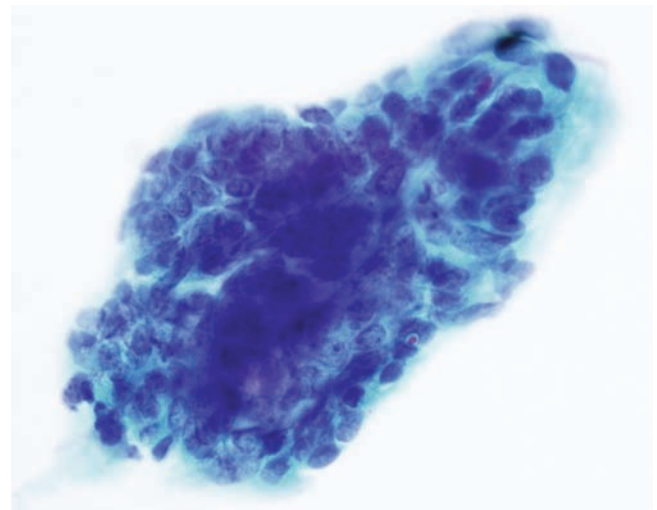


Figure 33 Metastatic colon adenocarcinoma. There are cohesive clusters of elongated cells with hyperchromatic nuclei and palisading. Dirty necrosis was present elsewhere on the smears (Papanicolaou stain; magnification, 600 $\times$).

21 cases of metastases to the thyroid gland in which only five patients had a known history of malignancy (71). Metastatic clear cell carcinoma of the kidney is especially difficult to distinguish from primary thyroid carcinoma with clear cell features (72). Immunohistochemistry, including demonstration of thyroglobulin and TTF-1 staining can help in establishing the diagnosis of a primary tumor. Granular RCC can cytologically mimic oncocyctic neoplasm; while plasmacytoma associated with amyloid may be misinterpreted as medullary carcinoma (73). Again, the utilization of immunohistochemical stains such as calcitonin, chromogranin, kappa, lambda, cytokeratin, and TTF-1 may be helpful in separating medullary carcinoma from plasmacytoma; while renal cell antigen, TTF-1 and thyroglobulin are helpful in the work-up of RCC. Recognition of metastatic malignancy can prevent unnecessary thyroidectomy, and appropriately direct the search for an unsuspected primary malignancy.

I. Ancillary Studies

Ancillary studies, especially immunohistochemistry, may prove valuable in the differential diagnosis of thyroid tumors, provided a cell block, thinly prepared smear, cytopins, liquid-based preparation, or tissue biopsy is available for evaluation (Table 9) (74). Only a few studies describing the utilization of molecular tests on thyroid FNA specimens have been reported. RET/PTC rearrangements and BRAF mutations have been reported to be useful as ancillary tests to cytology in selected cases, where they helped confirm the diagnosis of malignancy (75). However, we believe that currently, the diagnosis of malignancy should be established on the basis of cytomorphologic features.

J. Clinical Implications of an FNA Diagnosis

The majority (70–80%) of FNAs classified as FN are neoplastic on histologic follow-up. Using strict cytologic

Table 9 Selective Immunohistochemical Stains in the Differential Diagnosis of Thyroid Tumors

Papillary carcinoma, follicular neoplasm
Thyroglobulin +, TTF-1 +
Renal cell carcinoma
CD10+, EMA+, RCA+, TTF-1–, thyroglobulin–
Histiocytes and cyst lining cells:
CD68+, cytokeratin–
Endocrine tumors
Chromogranin+, synaptophysin+, thyroglobulin–; calcitonin+ (medullary carcinoma); PTH+ (parathyroid adenoma); S-100+ (sustentacular cells in paraganglioma)
Metastatic carcinoma
TTF-1+ and thyroglobulin– (lung); GCFP+ (breast); ER/PR+ (breast, ovary); PLAP+ (germ cell tumor); HepPar1+ (liver); PSA+ (prostate); S100+ and HMB 45+ (melanoma)

Abbreviations: EMA, epithelial membrane antigen; ER/PR, estrogen/progesterone receptor; GCFP, gross cystic fluid protein; PLAP, placental like alkaline phosphatase; PSA, prostate-specific antigen; PTH, parathyroid hormone; RCA, renal cell antigen; TTF-1, thyroid transcription factor-1; *Source:* Modified from Ref. 74.

Table 10 Assessment of Probability of Cancer Risk on Follow-up Thyroidectomies

FNA diagnosis	Cancer rate	Cancer risk(a)
Benign nonneoplastic	3%	—
Follicular lesion of undetermined significance	14%	5 X
Follicular neoplasm	33%	11 X
Suspicious for malignancy	56%	20 X
Malignant	100%	
Nondiagnostic/unsatisfactory	12%	

^aCancer risk is compared with benign nonneoplastic diagnosis.

Source: Modified from Ref. 17.

Table 11 Thyroid FNA Diagnoses and Suggested Management Options

FNA diagnosis	Management options
Benign/nonneoplastic	
Asymptomatic, <4 cm	Repeat US in 6 mo
Symptomatic or >4 cm	Consider lobectomy
Cyst, >2 recurrences	Consider lobectomy
Follicular lesion of undetermined significance	Repeat US in 6 mo or repeat FNA, if <4 cm. Consider lobectomy if larger.
Follicular neoplasm	Lobectomy
Suspicious for malignancy	Lobectomy or total thyroidectomy
Malignant	Total thyroidectomy
Nondiagnostic/unsatisfactory	Repeat FNA under US guidance
Multiple nondiagnostic samples	Consider lobectomy

Abbreviations: FNA, fine needle aspiration; US, ultrasonography;

Source: Modified from Ogilvie Ref. 2

criteria, diagnoses of FN and “FLUS” show cancer on histologic follow-up in 30% and 10% of cases, respectively. Cancer is found in 20% or less of these cases when using lax criteria and/or when FN is combined with other indeterminate diagnoses. It is important, therefore, to designate FN as a diagnostic category that is distinct from “cellular hyperplastic nodule” or other indeterminate follicular lesions, in our opinion. Most clinicians will recommend excision for FN and accept the fact that the cytologic diagnosis is probabilistic and that it may be benign on follow-up (23,76–78). Clinical follow-up or repeat FNA is recommended for those cases classified as “FLUS.”

Wu et al. examined 401 FNAs with follow-up surgical excision and calculated the cancer rates and risks associated with various cytologic diagnoses (17). Providing this data to clinicians and patients may be extremely helpful in deciding on management options (Tables 10 and 11). The estimated incidence of malignancy in patients who have thyroid nodules and no other associated risk factors is 9% to 13% (79).

K. Summary of Thyroid FNA

Thyroid FNA is primarily a screening tool; therefore, a conclusive diagnosis is not always required. The pathologist's role is to minimize the number of

indeterminate diagnoses without yielding unacceptably high rates of false-negative and false-positive diagnoses. FNA can assign diagnostic probabilities that would help guide patient management in many cases. Although the use of these “diagnostic categories” is encouraged, they should not be used alone. Diagnoses should be qualified, when applicable, with an appropriate differential diagnosis. Individual centers should monitor their own diagnostic accuracy and cancer risks and provide these data to their clinicians in order to help guide the management of their patients. Recommendations for follow-up may be included in the report, if acceptable to clinicians in your institution. The use of the terms “atypical” and “indeterminate” as stand-alone diagnoses is not recommended as their meanings are not standardized and may be interpreted in different ways. Close cooperation between pathologists and clinicians is essential so that the accuracy of the technique, terminology used in the report, and clinical implications of FNA are clearly defined.

II. PARATHYROID GLANDS

Parathyroid glands are seldom sampled by FNA, unless clinically presenting as a “thyroid nodule.” Parathyroid cysts and adenomas are the most commonly encountered lesions. Normal parathyroid glands show cytologic features similar to normal thyroid, i.e., monolayered sheets and loosely cohesive groups of intermediate-sized cells with honeycomb configuration and occasional microfollicle formation. In addition, many naked nuclei are usually present. The cells have delicate cytoplasm and round nuclei with inconspicuous nucleoli. In contrast to that of the thyroid gland, colloid is absent and lipid may be very noticeable in the background, especially in DQ smears.

Parathyroid cysts, when aspirated, have a very characteristic watery, clear consistency that is almost always diagnostic. This gross appearance should initiate hormonal analysis of the cyst fluid for parathyroid hormone assay (C-terminal specific) to confirm the diagnosis (66). Differential diagnosis includes cystic lesions of the thyroid (Table 6). These parathyroid cysts often represent cystic adenomas that are hormonally inactive; therefore, easily mistaken clinically for thyroid nodules (80). Cytologically, the cyst fluid may be acellular or show rare, degenerated groups of cells (81). A specific diagnosis of parathyroid cyst will enable appropriate treatment by complete fluid aspiration, which thereby eliminates the need for hormonal treatment or surgery in most cases (66).

Solid parathyroid adenomas yield highly cellular aspirates composed of clusters of uniform cells with round nuclei, finely to coarsely granular chromatin, and small distinct nucleoli (Fig. 34) (3). Occasional chief cells with an oncocyctic appearance are encountered. Anisonucleosis and many stripped nuclei in the background are commonly seen (82). Papillary clusters or microfollicles may be present, which can lead to a misdiagnosis of PTC or FN (83). Attention to the

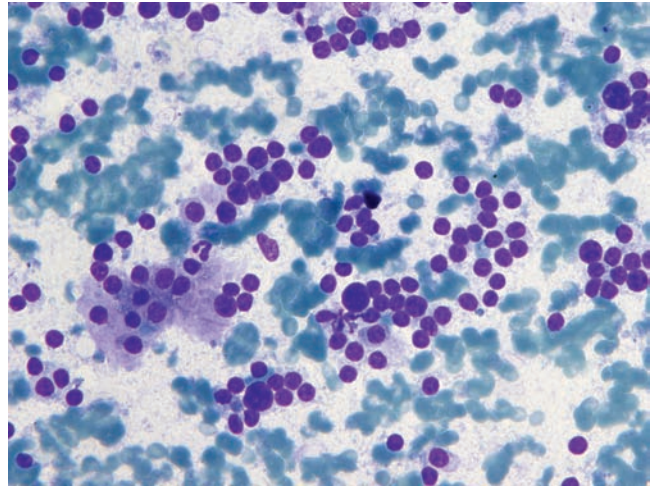


Figure 34 Parathyroid adenoma. The cells are uniform in appearance, have delicate cytoplasm, and show a suggestion of microfollicular architecture. Many stripped nuclei are found in the background. Occasional anisonucleosis is observed (DQ stain; magnification, 400 $\times$).

absence of nuclear features of papillary carcinoma should prevent a false-positive diagnosis of malignancy. Distinguishing parathyroid adenoma from thyroid FN, however, is more problematic (84). FNA cannot discriminate between parathyroid adenoma and parathyroid hyperplasia since clinical correlation is needed for such a distinction. *Parathyroid carcinoma* may show uniform cytologic appearance similar to adenoma or may display severe cytologic atypia and pleomorphism (Fig. 35) (41). Histologic confirmation is needed to confirm the diagnosis of malignancy.

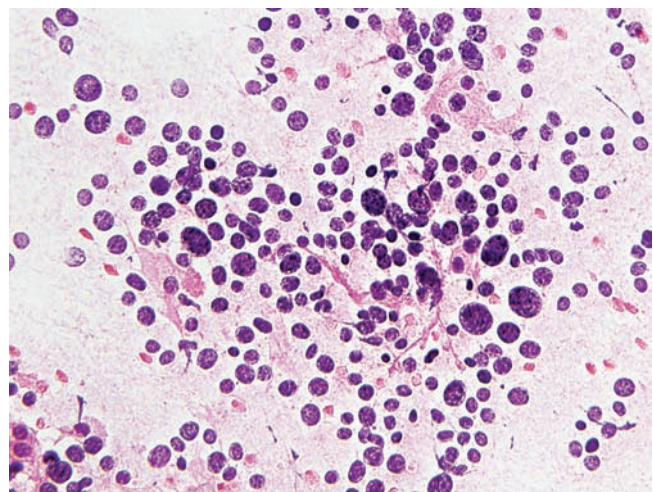


Figure 35 Parathyroid carcinoma. The aspirate is composed mostly of single cells with occasional loose clusters. There is severe cytologic atypia and extreme pleomorphism (H&E stain; magnification, 600 $\times$).

III. MAJOR SALIVARY GLANDS

A. Introduction

Although FNA has an established role in guiding patient management in many organ systems, the significance of its value in salivary gland tumors is surrounded by some controversy. Some investigators believe that FNA biopsy should not be used in the routine evaluation of salivary gland tumors (85). In their opinions, preoperative FNA cytologic diagnosis will not alter the management of patients or extent of surgery in most instances since it is the anatomic relation of the facial nerve to the parotid neoplasm that determines the extent of surgery, not the histologic classification. In addition, FNA may rarely induce marked necrosis and epimyoepithelial proliferation, possibly causing diagnostic problems on histology (86,87). Many institutions, however, use FNA in the initial work up of salivary gland enlargement (88–91). FNA has a documented role in distinguishing inflammatory from neoplastic disease, a differential that may not be resolved solely by clinical investigation. FNA has also an established role in distinguishing between benign and malignant neoplasms, metastatic versus primary malignancies, and confirming the recurrence of cancer. In addition, FNA is valuable in distinguishing neoplasms involving the submandibular gland or tail of parotid from enlarged lymph nodes.

Most studies report a diagnostic accuracy of 81% to 98% in the detection of malignant disease, with a specificity of 71% to 99% (92–94). Diagnostic accuracy, however, appears to increase with experience. Heller et al. evaluated 101 patients, assessing the impact of FNA on changing the clinical management; 35% of their patients had a change in the clinical approach as a result of preoperative FNA diagnoses (95). Surgery was entirely avoided in 27% of the patients, and a lesser surgical procedure was performed in another 8% of the patients. In seven patients, FNA indicated a need for surgery where clinically no surgery was planned. Cohen et al. reported that FNA was as accurate as frozen sections in rendering a correct diagnosis (96). Furthermore, FNA allowed for preoperative patient management and therapy planning and had an overall accuracy rate of 88%. Cystic salivary gland lesions were the most challenging on FNAs and frozens (97). Non-diagnostic FNA rates are approximately 10%, and false-negative and false-positive rates are reported to be on the order of 4.0% and 3.5%, respectively (98). O'Dwyer et al., however, reported a 25% false-negative rate in their series (99). The majority of false-negative diagnoses are either because of sampling error or misinterpretation. Interpretation errors are mostly associated with limited cellularity or neoplasms demonstrating bland cytology (98). Preoperative FNA diagnosis should probably be best interpreted in the context of the patient's clinical picture.

Cytology of Normal Salivary Glands

The specimens are usually of low cellularity and are composed of acinar and ductal cells. A slight amount of

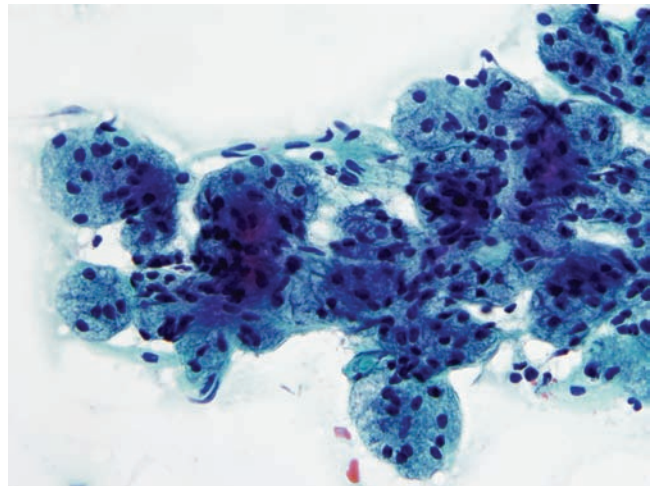


Figure 36 Benign acinar cells arranged in “rosette” formation. The cells have abundant foamy vacuolated cytoplasm with indistinct cell borders, and eccentric nuclei (Papanicolaou stain; magnification, 600×).

fat may be admixed with the epithelial cell clusters. The acinar cells have a characteristic “rosette” or “clustered ball” configuration (Fig. 36). The cells are large with abundant foamy vacuolated cytoplasm, indistinct cell borders, and eccentric nuclei. The nuclei are round with finely granular chromatin, and small or indistinct nucleoli. The ductal cells are arranged in monolayered sheets with a honeycomb configuration. They have scant delicate cytoplasm and round, uniform nuclei. Naked acinar cell nuclei may be seen in the background and should not be confused with lymphocytes (100). Cellular aspirates should not be confused with acinar cell carcinoma; the latter presents as flat and cohesive sheets of cells that lack the characteristic lobular or rosette configuration of benign acinar tissue.

B. Nonneoplastic Salivary Gland Lesions

A variety of nonneoplastic conditions may cause diffuse salivary gland enlargement or present as a mass lesion. Some patients have prominent salivary glands (*sialosis*), which present as diffuse enlargement, and show benign salivary gland elements on FNA (100).

Fatty Infiltration

Fatty infiltration of the salivary glands also presents as a diffuse enlargement. Cytologically, in addition to normal salivary gland elements, there is significant increase in the amount of adipose tissue situated between ductal and acinar cells (101). Sialosis and fatty infiltration have been associated with diabetes, cirrhosis, alcoholism, medications, nutritional deficiencies, and hormonal disturbances (102).

Sialadenitis

Acute sialadenitis. Acute sialadenitis is seldom sampled, and these patients are typically tender to

palpation and aspiration. Many neutrophils are admixed with benign salivary gland elements. Reactive and reparative changes may be seen, as well as fragments of stone (98).

Chronic sialadenitis. Chronic sialadenitis commonly results from stones or postsurgical scarring and is more frequently seen in the submandibular gland. The aspirates are usually of low cellularity and show predominance of ductal cells (secondary to acinar atrophy and ductular proliferation). The background has variable number of lymphocytes, occasional plasma cells and neutrophils, and spindle fibroblasts (Fig. 37). Squamous and mucinous metaplasia may be focally encountered (Fig. 38) (103).

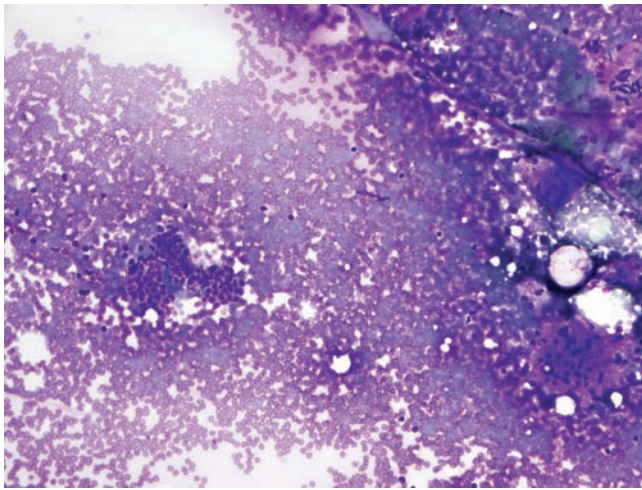


Figure 37 Chronic sialadenitis characterized by low cellularity and admixture of ductal and acinar cells. Inflammatory cells and fibroblasts are present in the background (DQ stain; magnification, 200×).

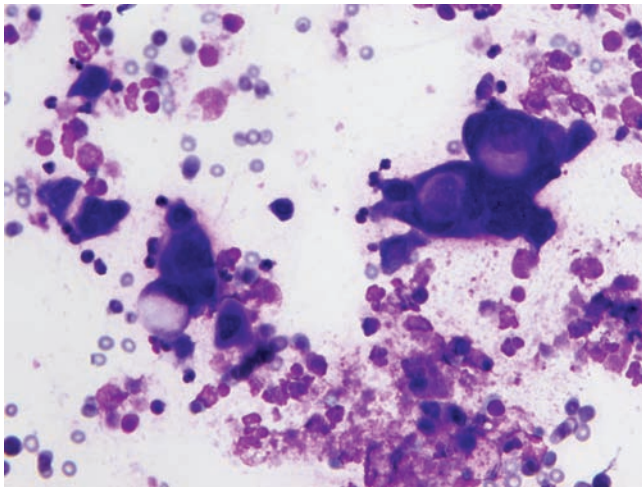


Figure 38 Chronic sialadenitis associated with squamous and mucinous metaplasia. There is mild atypia, which is reactive and degenerative in nature (DQ stain; magnification, 400×).

Atypia, if present, is reactive and degenerative in nature. Differential diagnosis of chronic sialadenitis includes benign lymphoepithelial lesion (lymphoepithelial sialadenitis), Warthin tumor, and mucoepidermoid carcinoma (see lymphoid-rich lesions) (104).

C. Cystic Lesions

Nonneoplastic cysts present as mass lesions and may be congenital or a result of duct obstruction (retention cyst) (105).

Retention cyst. Retention cyst is the most common cause of benign cysts in the salivary glands and is a true cyst, i.e., lined by ductal epithelium. Grossly, the aspirates have a watery, mucoid consistency. The aspirates are of low cellularity and consist mostly of proteinaceous mucoid material mixed with histiocytes and few inflammatory cells. The ductal cells typically show degenerative features (smudgy nuclei) and may have a cuboidal or metaplastic squamous appearance. Complete disappearance of the mass following aspiration is supportive but not diagnostic of retention cyst, as a number of neoplasms (especially low-grade mucoepidermoid carcinoma) may present with a prominent cystic component (Table 12). Therefore, a descriptive diagnosis is warranted in these conditions, with recommendations for clinical correlation and follow-up. Re-aspiration of any residual mass following evacuation of the cystic component is necessary, in order to avoid a potential false-negative diagnosis.

Branchial cleft cyst. Branchial cleft cyst is the most common cystic lesion of the lateral neck and is usually located on the anterior border of sternocleidomastoid muscle. It has also been encountered in and around the parotid glands and in the floor of mouth. Cytologically, it is indistinguishable from epidermoid cyst. The smears consist predominately of anucleated and nucleated squamous cells, and variable number of neutrophils (Fig. 39). Lymphocytes are not commonly seen. Significant atypia may be appreciated, especially if the cyst is secondarily infected (Fig. 40). The atypia, however, is degenerative in nature and is characterized by smudgy nuclei, low nuclear-to-cytoplasmic ratios, and variably faint to dense cytoplasm (106). However, extreme caution must be exercised in these cases in order to avoid overdiagnosing or underdiagnosing metastatic squamous carcinoma.

Squamous carcinoma. Squamous carcinoma may occasionally show minimal atypia, and can be indistinguishable from an inflamed branchial cleft cyst. A definitive diagnosis of malignancy, therefore, should

Table 12 Differential Diagnosis of Salivary Gland Cystic Lesions

Retention cyst
Branchial cleft cyst
Epidermoid cyst
Lymphoepithelial (HIV-associated) cyst
Pleomorphic adenoma
Warthin tumor
Mucoepidermoid carcinoma, low grade
Papillary cystic acinar cell carcinoma
Metastatic keratinizing squamous cell carcinoma

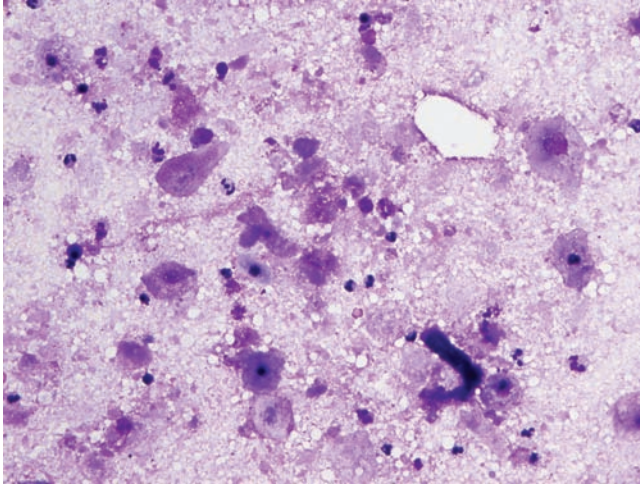


Figure 39 Branchial cleft cyst. There are many anucleated and nucleated squamous cells and few neutrophils (DQ stain; magnification, 400×).

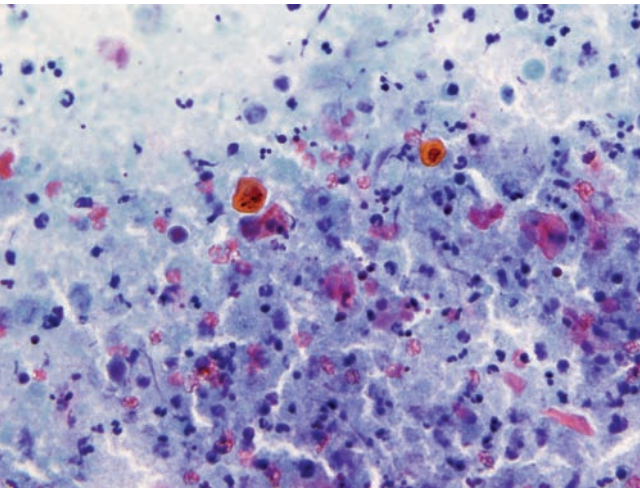


Figure 40 Branchial cleft cyst showing inflammatory atypia, characterized by degenerated keratinized squamous cells. Many neutrophils are present in the background. Metastatic squamous carcinoma may have an identical appearance (Papanicolaou stain, 400×).

only be established in the presence of clusters and sheets of atypical squamous epithelium (Fig. 41), or singly scattered markedly atypical keratinized cells (Fig. 42). Cytologic features found to be more supportive of squamous carcinoma, compared with branchial cleft cyst, are the presence of necrotic debris and fewer neutrophils. We usually do not issue a diagnosis favoring branchial cleft cyst in patients older than 25 years, but rather provide a descriptive diagnosis of “cystic squamous lesion without significant atypia,” and provide an appropriate differential diagnosis including cystic squamous carcinoma (106,107).

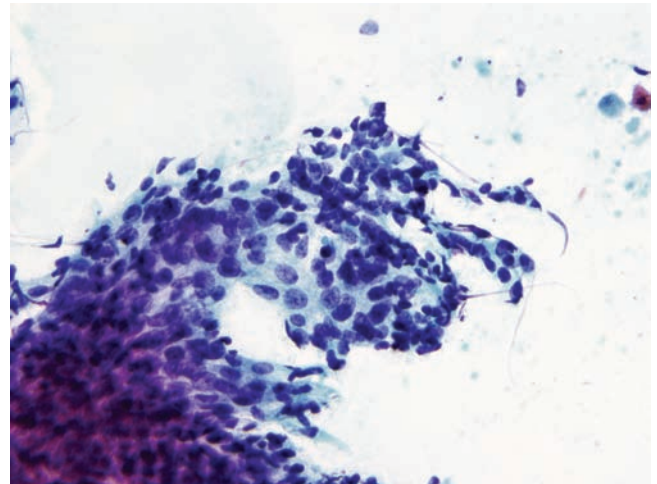


Figure 41 Squamous carcinoma demonstrating clusters and sheets of atypical epithelial cells (Papanicolaou stain, 400×).

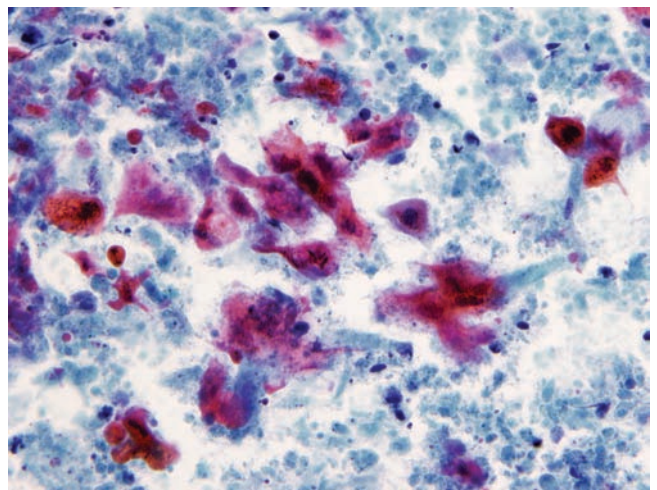


Figure 42 Metastatic squamous carcinoma showing singly scattered markedly atypical keratinized cells (Papanicolaou stain, 600×).

Warthin tumor. Warthin tumor may be associated with squamous metaplasia and extensive cystic change, including atypical metaplasia, which can be confused with metastatic squamous carcinoma; therefore, search and recognition of the dual population of oncocytes and lymphoid cells in the smears should establish the correct diagnosis. Lymphoepithelial cysts are further discussed with lymphoid-rich lesions.

D. Salivary Gland Neoplasms, Interpretation Challenges, and a Morphologic Approach to the Diagnosis

Salivary gland FNA is probably one of the most challenging area in cytology, as it can be difficult to

render a specific diagnosis. This is due to the wide assortment of neoplasms arising in these organs, their relative rarity, and variability in their cytologic appearances (98). Histologic diversity may even occur within the same neoplasm. Diagnostic difficulties are encountered mostly with cystic lesions, as previously discussed, and with low-grade malignancies, cellular benign neoplasms, atypical inflammatory and lymphoid lesions, and rarely encountered lesions (92,108). Occasionally, an unusual cytologic presentation of a common tumor also presents a challenge. While FNA diagnosis of high-grade malignancy is usually straight forward, distinguishing low-grade malignancies from benign neoplasms and some inflammatory processes may at times be problematic (109).

The more commonly encountered benign neoplasms include pleomorphic adenoma, basal cell adenoma, and Warthin tumor (110). Primary malignant salivary gland neoplasms are subdivided into low grade and high grade. Common low-grade malignancies include mucoepidermoid carcinoma (MEC) and acinic cell carcinoma. High-grade malignancies include adenoid cystic carcinoma (ACC), high-grade MEC, squamous cell carcinoma, salivary duct carcinoma, and poorly differentiated carcinoma, not otherwise specified. Metastatic malignancies involving the salivary glands include malignant melanoma and squamous cell carcinoma. The salivary glands may also be involved primarily or secondarily by malignant lymphoma.

The cytologic features of salivary gland tumors, as well as some of the more commonly encountered problems and pitfalls associated with FNA interpretations are presented in this chapter. Strict and well-defined cytologic and architectural criteria that help facilitate arriving at the proper diagnosis are discussed in depth. The clinical significance of a precise cytologic diagnosis is highlighted. The role of ancillary studies such as immunocytochemistry and flow cytometry is presented where appropriate. The traditional approach of describing nonneoplastic and inflammatory salivary gland lesions followed by benign and malignant neoplasms, as presented in most textbooks, is not followed in this discussion. Rather, we believe that subdividing salivary gland tumors into defined cytomorphologic groups is a more practical approach (Table 13) (111). Four of these categories are based on cell size, amount of cytoplasm, degree of cytologic atypia, and the nature of background. These categories include tumors with small cell size (basaloid), intermediate-sized cells with low-grade cytologic features, large cells with abundant cytoplasm, and lymphoid-rich lesions (Table 13). A fifth category is dedicated to pleomorphic adenoma, the most commonly encountered neoplasm in salivary

Table 13 Differential Diagnostic Categories in Salivary Gland FNA

Neoplasms with basaloid cell features
Tumors with intermediate-sized cells and bland cytology
Tumors characterized by large cells and abundant cytoplasm
Lesions rich in lymphocytes
Variable cytologic appearances of pleomorphic adenoma

Table 14 Differential Diagnosis of Basaloid Neoplasms in Salivary Glands

Basaloid neoplasms with significant cytologic atypia ^a	Basaloid neoplasms without significant cytologic atypia
ACC, cribriform ^b , and solid Basal cell adenocarcinoma	ACC, cribriform ^b , and solid Basal cell adenoma
Basaloid squamous cell carcinoma, metastatic	Basal cell adenocarcinoma
Poorly differentiated carcinoma, not otherwise specified	Cellular pleomorphic adenoma
Neuroendocrine carcinoma	Epithelial-myoepithelial carcinoma
Pilomatrixoma	Polymorphous low-grade adenocarcinoma
Metastatic carcinoma, including cutaneous basal cell carcinoma, thyroid, breast, and lung	Pilomatrixoma
	Metastatic carcinoma

^aSignificant cytologic atypia is characterized by the presence of moderate to marked nuclear pleomorphism and/or large prominent nucleoli. Small nucleoli may be seen in basal cell adenoma.

^bCribriform ACC may or may not show significant cytologic atypia, but the combined architectural features of microcyst formation and hyaline globules are usually diagnostic.

glands and its tendency for cytologic diversity and mimicry of other neoplasms. This simplified approach will emphasize differential diagnoses of tumors that share similar cytomorphologic features and help identify limitations associated with FNA.

E. Salivary Gland Neoplasms with Basaloid Cell Features

Salivary gland neoplasms with basaloid cell features are a relatively uncommon and heterogeneous group of tumors characterized by small cells, presenting mostly in cohesive clusters. Most notable of these neoplasms are ACC and basal cell adenoma. FNA cytology of these tumors is seldom described in the literature. The rare reports available emphasize the difficulty in making a precise diagnosis. Appreciation of the architectural features and nuclear atypia are most important for evaluating basaloid tumors (Table 14).

Basal Cell Adenoma

Basal cell adenoma is an uncommon benign neoplasm accounting for approximately 2% of salivary gland tumors. Four architectural patterns are histologically described, including solid, trabecular, tubular, and membranous (110). These patterns, for the most part, are not reproducible on FNA. Cytologic features include the presence of tightly cohesive clusters of basaloid cells with numerous naked nuclei in the background (Fig. 43) (112). The clusters may have sharp smooth community borders, show a trabecular or jigsaw puzzle configuration, or display branching and budding (113). The basaloid cells have scant cytoplasm, round to oval nuclei, and finely to coarsely granular chromatin (Fig. 44) (114,115). The membranous variant of basal cell adenoma often displays prominent dense

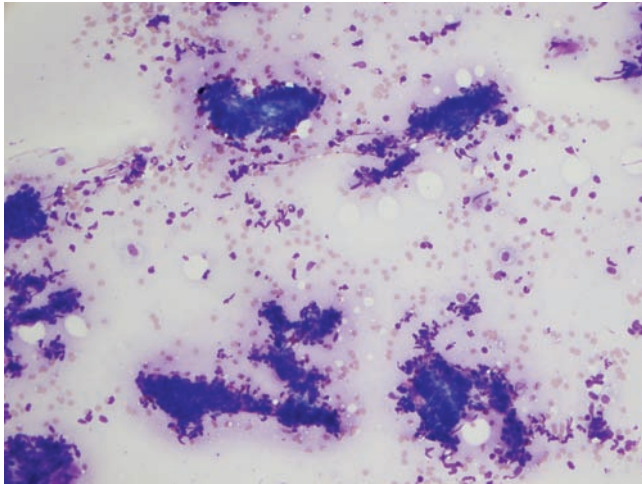


Figure 43 Basal cell adenoma. Tightly cohesive clusters of basaloid cells and many background stripped nuclei (DQ stain, 200 $\times$).

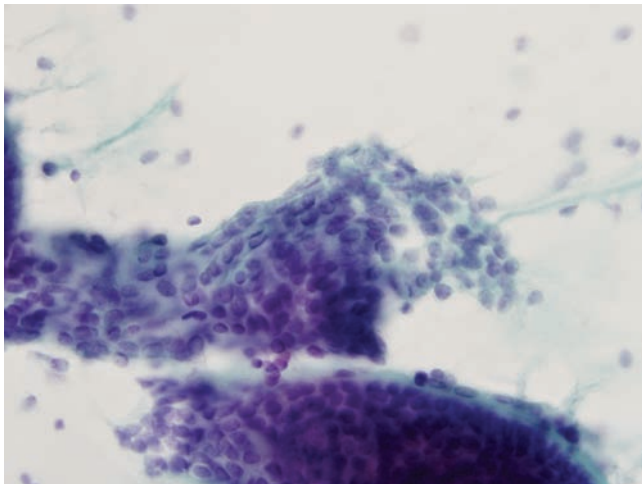


Figure 44 Basal cell adenoma. The basaloid cells have scant cytoplasm, round to oval nuclei, and finely to coarsely granular chromatin (Papanicolaou stain, 600 $\times$).

extracellular material (stains hyaline pink with DQ, and green with Papanicolaou), corresponding to reduplicated basal lamina, surrounding the cell clusters (Fig. 45) (116). The solid variant of basal cell adenoma consists mostly of large flat and cohesive sheets of basaloid cells. Canalicular adenoma is reported to show clinical as well as cytologic features similar to basal cell adenoma (117).

Adenoid Cystic Carcinoma

ACC is the most common of these basaloid tumors and is the main entity to be considered in the differential diagnosis of basal cell adenoma. It accounts for approximately 3% to 5% of major salivary gland tumors and is

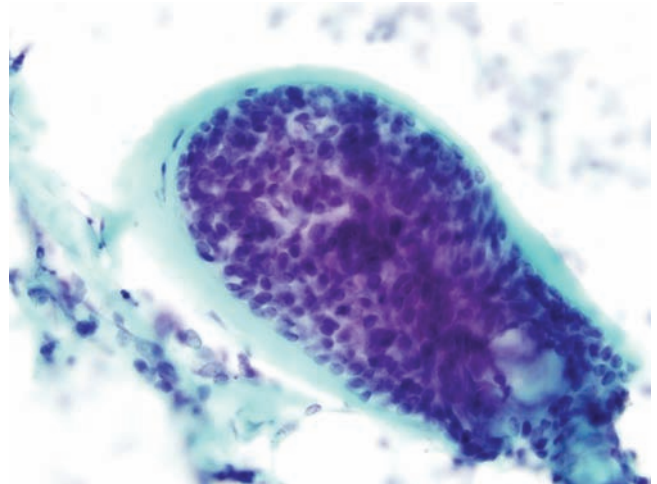


Figure 45 Membranous variant of basal cell adenoma. There is dense hyaline extracellular material surrounding the basaloid cell clusters. Note the sharp interface between the stromal material and cells (Papanicolaou stain, 400 $\times$).

the third most common malignancy in salivary glands (following MEC and acinic cell carcinoma) (110). The cribriform (well differentiated) variant of ACC is the most frequently encountered type, and is the easiest to distinguish from basal cell adenoma (111). Solid variant of ACC, on the other hand, is rarely encountered, and may not be possible to separate from basal cell adenoma. Cribriform ACC consists of broad cohesive sheets of basaloid cells with prominent microcystic spaces containing globules of homogenous acellular hyaline material. These hyaline globules are numerous, large, variable in size, shaped as spheres and bands, and have smooth contours (Fig. 46). The globules may

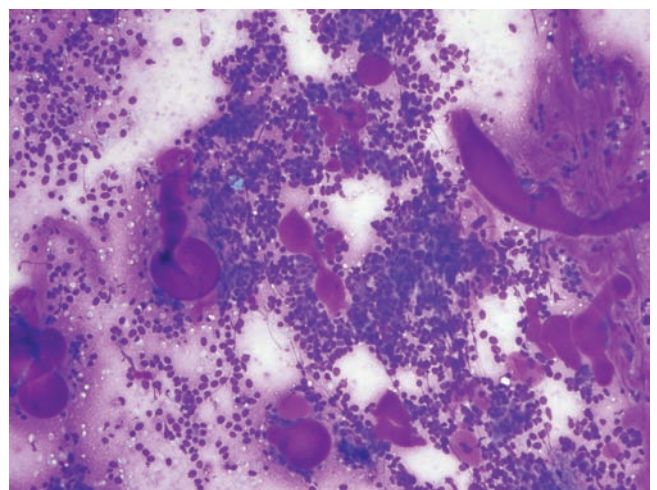


Figure 46 Adenoid cystic carcinoma, cribriform type. Broad cohesive sheets of basaloid cells associated with numerous hyaline globules. The globules are large, variable in size, and shaped as spheres and bands (DQ stain, 200 $\times$).

be associated with the basaloid cells or lie freely in the background, and stain purple red with DQ, or pale gray with Papanicolaou (Figs. 47 and 48). The basaloid cells may show nuclear and cytoplasmic features similar to basal cell adenoma, including oval hyperchromatic nuclei with finely to coarsely granular chromatin and scant cytoplasm; but may illustrate more pronounced atypia and prominent nucleoli (Fig. 48). Solid ACC is characterized by paucity or absence of

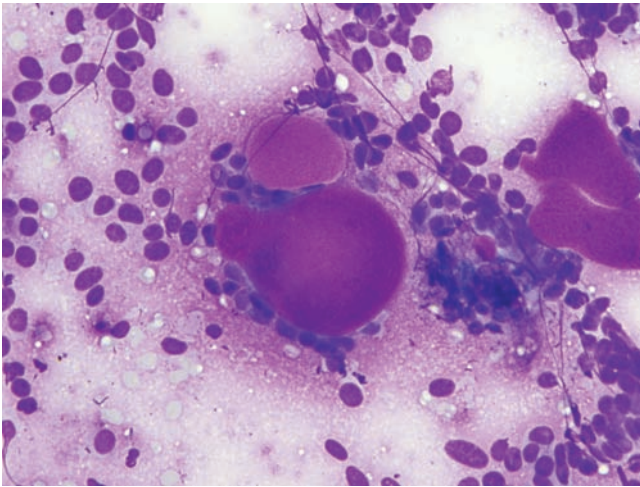


Figure 47 Adenoid cystic carcinoma, cribriform type. The hyaline globules are acellular, have a smooth outer border, and show a sharp interface with surrounding basaloid cells (DQ stain, 400 $\times$).

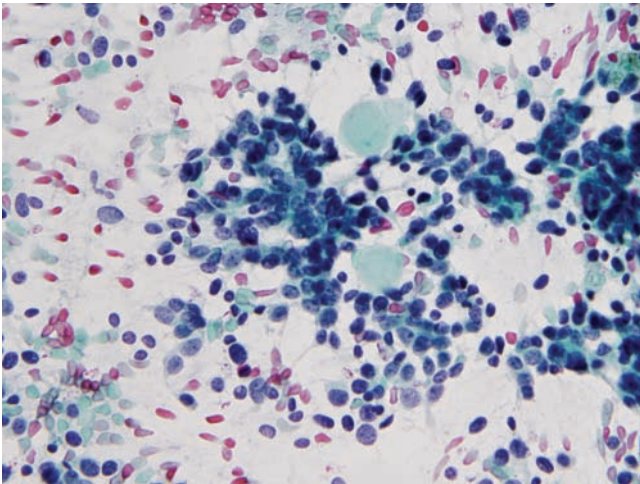


Figure 48 Adenoid cystic carcinoma, cribriform type. The neoplastic cells have oval to round hyperchromatic nuclei with finely to coarsely granular chromatin and scant cytoplasm. They are associated with hyaline globules, which stain pale gray-green in this preparation. Naked nuclei are observed in the background (Papanicolaou stain, 400 $\times$).

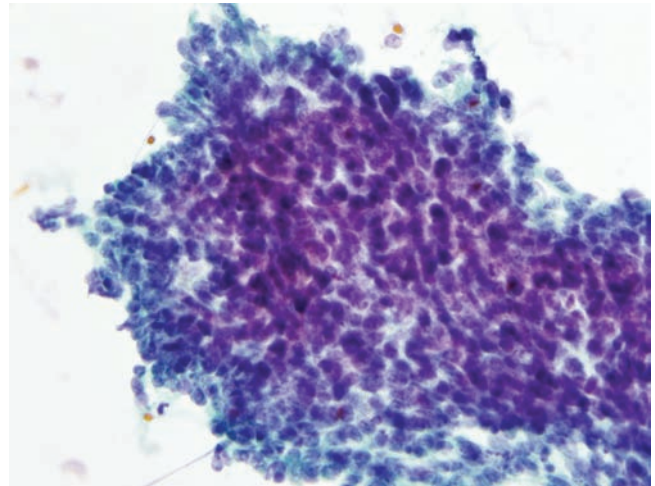


Figure 49 Metastatic basaloid squamous carcinoma. The smears showed many tightly cohesive clusters of basaloid cells with significant cytologic atypia. This appearance may be indistinguishable from solid variant of adenoid cystic carcinoma and other malignant basaloid tumors (Papanicolaou stain, 400 $\times$).

microcystic spaces and hyaline globules and moderate to severe cytologic atypia, which should prompt a malignant diagnosis. However, we have encountered several cases of solid ACC that lacked significant cytologic atypia and showed features identical to the solid variant of basal cell adenoma. Therefore, in our experience, in the absence of atypia, FNA cannot separate between solid basal cell adenoma and solid ACC (113). A malignant diagnosis can be rendered in the presence of significant atypia, but it may be extremely difficult to distinguish solid ACC from metastatic basaloid squamous cell carcinoma (Fig. 49) (118).

Basal Cell Adenocarcinoma

Basal cell adenocarcinoma shows low power architectural features highly reminiscent of basal cell adenoma, including tightly cohesive clusters of basaloid cells with papillary and filiform architecture (119). Although, often there is associated significant cytologic atypia and mitotic activity, some cases lack atypia. The diagnosis of basal cell adenocarcinoma is confirmed histologically by demonstration of parenchymal and soft tissue invasion; therefore, it should be considered in the FNA differential diagnosis of all basaloid tumors.

Primary Small Cell Carcinoma/Neuroendocrine Carcinoma

Primary small cell carcinoma/neuroendocrine carcinoma is cytologically identical to its pulmonary counterpart; therefore, a metastatic lung carcinoma should first be excluded (120). FNA shows a predominately dissociative cell pattern and few cohesive clusters. The neoplastic cells have hyperchromatic nuclei and minimal amount of cytoplasm, and may show cigar-shaped nuclei and prominent nuclear molding.

Metastatic Carcinoma

Metastatic carcinoma from various sites, such as breast, thyroid and head and neck, may also masquerade as a primary basaloid neoplasm, especially if prepared with a thin layer methodology (prominent shrinkage of the neoplastic cells gives them a basaloid appearance) (113). It is important, therefore, to consider the possibility of metastasis and inquire about previous history of malignancy.

Pilomatrixoma

Pilomatrixoma may be misdiagnosed as a basal cell tumor or small blue-cell tumor of childhood if the basaloid cells predominate in the aspirate. It is a benign neoplasm that mostly arises in the head and neck region of children. The finding of sheets of ghost squamous cells combined with basaloid cells is diagnostic of this lesion (121,122). Attention to the young age of the patient and careful search for the diagnostic ghost cells should prevent a potential false-positive diagnosis (111).

Cellular Pleomorphic Adenoma

Cellular pleomorphic adenoma is also included in the differential diagnosis of basal cell tumors and shows broad loosely cohesive clusters of intermediate-sized cells with haphazard nuclear arrangement and indistinct community borders (123). This is in contrast to basal cell tumors, which show tightly cohesive clusters of small basaloid cells with sharp community borders. Pleomorphic adenoma, in addition, demonstrates background plasmacytoid appearing cells in contrast to the naked nuclei associated with basal cell adenoma and ACC.

In summary, neoplasms with basaloid cell features represent one of the most challenging problems in salivary gland cytology. Depending on the presence or absence of significant cytologic atypia, several entities should be considered in the differential diagnosis (Table 14). In the absence of atypia, it is not possible to cytologically distinguish between solid ACC, basal cell adenoma, and basal cell adenocarcinoma. In the presence of significant atypia, it may not be possible to distinguish between solid ACC, basal cell adenocarcinoma, and basaloid squamous carcinoma. FNA, however, can be reliable in diagnosing cribriform ACC only if it shows prominent microcyst formation in association with numerous hyaline globules that are large, variable in size, have smooth contours, and shaped as spheres and bands. The mere presence of extracellular matrix in conjunction with basaloid cells does not establish a diagnosis of ACC, as extracellular matrix may be associated with other tumors such as basal cell adenoma, pleomorphic

Table 15 Stroma-Rich Salivary Gland Tumors

Pleomorphic adenoma
Basal cell adenoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial myoepithelial carcinoma

adenoma, basal cell adenocarcinoma, epithelial myoepithelial carcinoma, and polymorphous low-grade adenocarcinoma (PLGA) (Table 15). Hyaline globules in these latter tumors are usually focal, small, uniform in size, and have irregular contours (111). Careful attention to the tinctorial quality and shape of the stromal material and related neoplastic cells are helpful clues to establishing the appropriate diagnosis (98).

F. Salivary Gland Tumors with Intermediate-Sized Cells and Bland Cytology

This group of lesions is characterized by intermediate-sized cells with moderate amount of cytoplasm and minimal cytologic atypia (Table 16). Because of their bland cytology, they may be misinterpreted as benign neoplasms. In most instances, distinguishing cellular benign neoplasm from low-grade malignancy does not alter patient management as conservative surgery is indicated in both instances. However, it is appropriate to render a relevant differential diagnosis when the cytologic features are not diagnostic of a specific entity.

Low-grade MEC

MEC is the most common malignancy involving the salivary glands, and represents approximately 30% of salivary gland cancers. It occurs among all age groups with a peak incidence in individuals aged 20 to 40 years old (110). It is important to cytologically distinguish low-grade MEC from high-grade MEC because of the difference in their prognosis (90% and 40% 5-year survival, respectively). Low-grade MEC may be easily misinterpreted on FNA as a benign neoplasm because of its bland cytology. Diagnostic accuracy of MEC ranges from 33% to 75%, which is much lower than the overall accuracy of salivary gland FNA (73–90%).

Low-grade MEC is commonly cystic and is cytologically characterized by an admixture of glandular and metaplastic squamous cells (124–126). The background demonstrates mucinous material and debris (Fig. 50). The glandular cells may have a ductal appearance (intermediate cells) or may resemble macrophages (mucin-producing cells) (Figs. 51 and 52). Metaplastic cells are polygonal in shape and resemble immature metaplastic squamous cells and oncocytes (Fig. 51). They have dense cytoplasm, round nuclei, and prominent nucleoli. Variable cytoplasmic vacuolization may be observed. However, keratinized epidermoid cells are not usually seen in low-grade MEC. The predominance of mucin-producing cells in an aspirate may lead to a

Table 16 Salivary Gland Tumors with Intermediate-Sized Cells and Bland Cytology (Includes Squamous and Cystic Lesions)

Low-grade mucoepidermoid carcinoma
Polymorphous low-grade adenocarcinoma
Pleomorphic adenoma
Low-grade salivary duct carcinoma
Epithelial-myoepithelial carcinoma
Branchial cleft cyst and retention cyst
Neoplasms with a cystic component
Metastatic keratinizing squamous cell carcinoma
Squamous metaplasia in chronic sialadenitis, Warthin tumor and pleomorphic adenoma

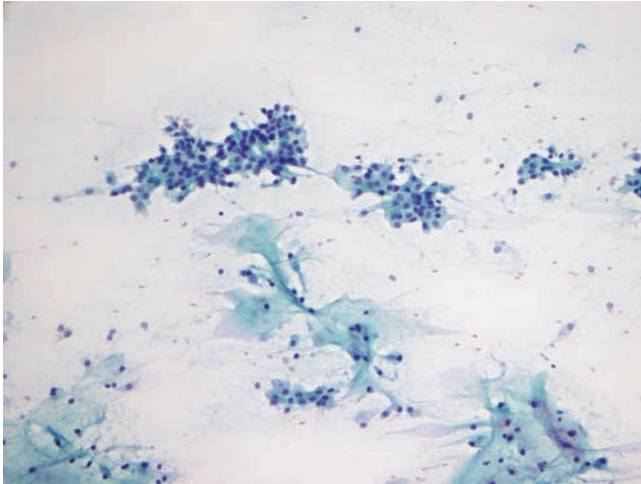


Figure 50 Low-grade MEC with prominent mucinous background and admixed neoplastic cells. The mucin has a stringy appearance (Papanicolaou stain, 200×).

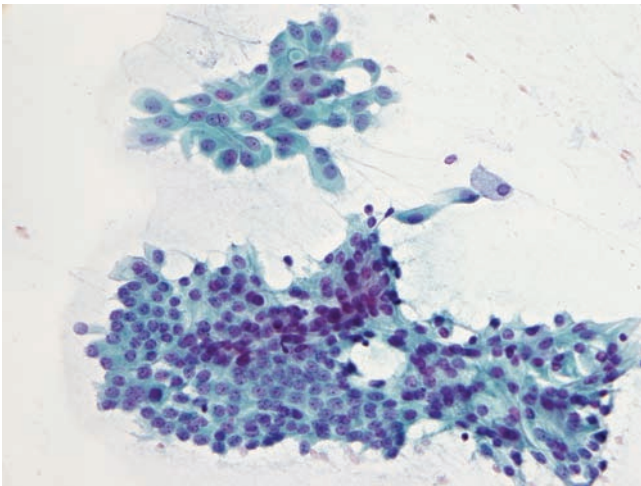


Figure 51 Low-grade MEC showing admixture of intermediate cells and metaplastic appearing cells. Intermediate cells have moderate delicate cytoplasm, round nuclei, and small nucleoli. The metaplastic cells have more abundant and denser cytoplasm, and prominent nucleoli. There is focal cytoplasmic vacuolization (Papanicolaou stain, 400×).

false-negative diagnosis of macrophages associated with benign cyst contents (124,127). The predominance of the glandular cells with their bland cytology can be easily mistaken for the epithelial component of pleomorphic adenoma (98). Also, the mucinous material in the background may be misinterpreted as the myxoid stromal component of pleomorphic adenoma (128). The presence of small nucleoli and the stringy nature of mucin admixed with macrophages favor MEC (Fig. 50). The general absence of nucleoli and the fibrillary myxoid nature of stroma admixed with spindle cells favor pleomorphic adenoma (111).

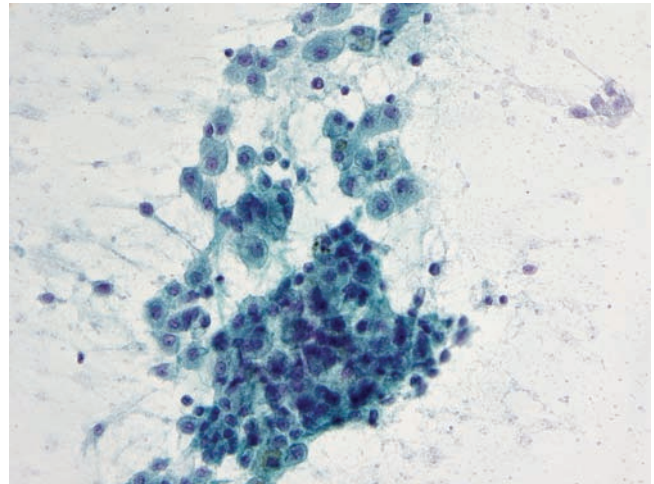


Figure 52 Low-grade mucoepidermoid carcinoma. Mucin producing cells and intermediate cells. The mucin producing cells resemble macrophages (Papanicolaou stain, 400×).

Polymorphous Low-Grade Adenocarcinoma

PLGA (terminal-duct carcinoma) may be difficult to cytologically differentiate from low-grade MEC (111). This is a low-grade adenocarcinoma, arising almost exclusively in the minor salivary glands (especially the palate) (129). Aspirates consist of sheets and three-dimensional clusters of intermediate-sized cells with moderate amount of delicate cytoplasm, uniform round to oval nuclei and finely granular chromatin (130–132). Nucleoli are inconspicuous. Acinar formation with overlapping of nuclei may be appreciated. A DQ stain may show purple extracellular material formed as dense stromal spheres, which can lead to confusion with the hyaline globules of ACC (133–135).

Lesions Containing Squamous Cells

Other lesions containing squamous cells should be considered in the differential diagnosis also (Table 17) (103). Squamous and mucus metaplasia in chronic sialadenitis can raise concerns for a low-grade MEC (Fig. 38). These specimens, however, are usually sparsely cellular and show admixture of benign ductal and acinar cells, in addition to background inflammation and fibroblasts. The occasional presence of degenerated epithelial cells of ductal origin (cuboidal cells or squamous metaplasia) in retention cyst may also raise the suspicion of low-grade MEC, but the sparse cellularity of the specimen and disappearance of mass after aspiration are features that favor a benign cyst.

Table 17 Salivary Gland Lesions Containing Squamous Cells

Mucoepidermoid carcinoma
Squamous cell carcinoma
Squamous metaplasia associated with Warthin tumor,
pleomorphic adenoma, chronic sialadenitis
Lymphoepithelial cyst
Branchial cleft cyst

Other cystic lesions that enter into the differential diagnosis include branchial cleft cyst and epidermoid cyst (Table 12).

G. Salivary Gland Neoplasms Characterized by Large Cells and Abundant Cytoplasm

These neoplasms may have bland cytology or show severe cytologic atypia and are subdivided according to the degree of atypia (Table 18). Tumors with oncocytic and/or clear cell features are also included in this group. Some of these neoplasms may show papillary, cystic, or cribriform architecture. Generally, the greatest challenge is encountered with tumors showing no significant atypia, as it may be extremely difficult to distinguish low-grade malignancies from benign neoplasms or discriminate among the various types of low-grade malignancies. The presence of severe atypia readily establishes the diagnosis of malignancy, but it may not be able to establish the specific type of malignancy.

High-Grade MEC

High-grade MEC has a less prominent cystic component and greater degree of atypia, compared with low-grade MEC. High-grade MEC is cytologically characterized by large pleomorphic cells with predominantly epidermoid or undifferentiated cell features (Fig. 53) (104). Glandular cells are rarely seen in high-grade MEC, but their presence in association with squamous cells establishes the diagnosis. The presence of marked keratinization is seldom observed in MEC; therefore, its presence favors metastatic squamous cell carcinoma from the oral cavity or upper respiratory tract (Fig. 42) (124,126,136). Primary squamous carcinoma of the salivary glands is very rare, accounting for less than 1% of salivary gland tumors and is indistinguishable cytologically from metastatic squamous carcinoma. Primary malignancies may also present as a malignant component of carcinoma ex pleomorphic adenoma or as a hybrid carcinoma with other malignancies such as

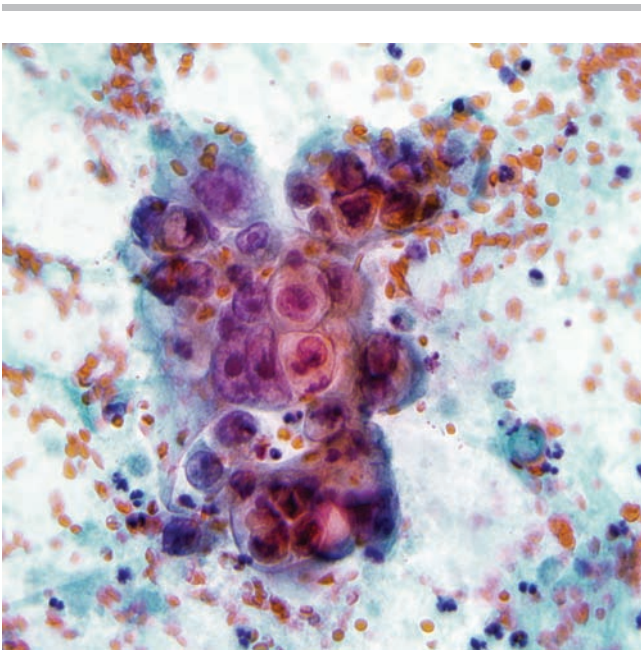


Figure 53 High-grade mucoepidermoid carcinoma. The cells are large, pleomorphic and show severe cytologic atypia. The cytoplasm has a dense quality with squamoid features (Papanicolaou stain, 600×).

ACC, mucoepidermoid carcinoma, and squamous carcinoma (137–140). In the latter cases, aspirates will demonstrate admixed but distinctive cytologic features of those neoplasms.

Salivary Duct Carcinoma

Salivary duct carcinoma (SDC) is a rare primary salivary gland malignancy characterized by its histologic resemblance to in situ and invasive ductal carcinoma of the breast. High-grade SDC is the most common subtype (>90% of cases) and considered one of the most aggressive salivary gland malignancies; while low-grade SDC is believed to carry a favorable prognosis (141–143). Architecturally, SDC shows a spectrum of cytologic findings, including broad flat sheets and three-dimensional tightly cohesive clusters of large monomorphic polygonal cells with abundant eosinophilic cytoplasm, round to oval hypochromatic nuclei, and prominent nucleoli. Medium-sized low columnar cells with central or eccentric hyperchromatic nuclei may be found. Occasional cribriforming and papillary configurations are seen. In low-grade SDC, the neoplastic cells have a uniform appearance and show minimal atypia. High-grade SDC shows moderate to severe nuclear atypia and pleomorphism (Fig. 54); however, the atypia can be random or focal in distribution (144–146). The presence of associated necrosis in the background constitutes an important clue to the diagnosis of high-grade SDC (Fig. 55). Occasionally, FNA may sample a more undifferentiated component of SDC in which case differentiating it from other high-grade carcinomas

Table 18 Salivary Gland Tumors with Large Cells and Abundant Cytoplasm (includes oncocytic and clear cell lesions)

With significant atypia ^a	Without significant atypia
High-grade mucoepidermoid carcinoma	Acinic cell carcinoma
High-grade salivary duct carcinoma	Oncocytic neoplasms, including Warthin tumor and oncocytoma
Radiation-induced sialadenitis	Low-grade salivary duct carcinoma
High-grade adenocarcinoma, NOS	Epithelial-myoepithelial carcinoma
Metastatic carcinoma, including breast, prostate, lung	
Hyalinizing clear cell adenocarcinoma	

^aSignificant atypia is defined as focal or diffuse moderate-severe nuclear atypia and pleomorphism.

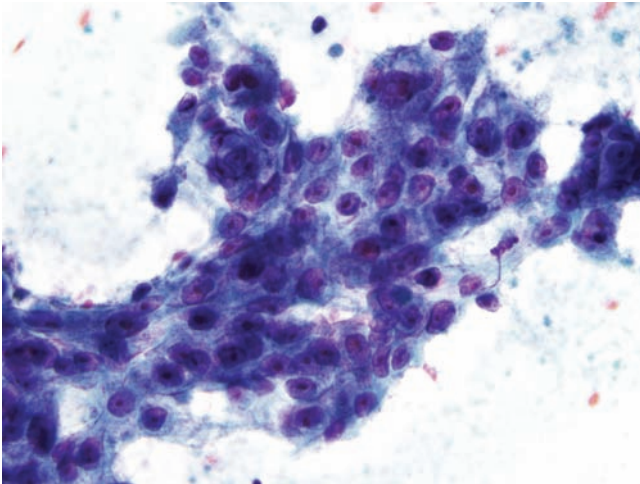


Figure 54 High-grade salivary duct carcinoma. There are flat sheets of epithelial cells with abundant delicate cytoplasm and moderate nuclear atypia. The nuclei are round to oval in shape and show finely granular chromatin and prominent nucleoli. (Papanicolaou stain, 600 $\times$).

may not be possible. High-grade MEC is the most difficult neoplasm to cytologically distinguish from high-grade SDC, since the latter is composed of large epithelial cells that resemble the nonkeratinizing component of MEC (145). The presence of undifferentiated intermediate squamous cells, poorly differentiated squamous cells, and mucus producing cells in addition to lack of papillary and cribriform configuration favors MEC (Table 19) (144). Furthermore, the atypia in MEC tends to be more pleomorphic and diffuse in nature, whereas the atypia in high-grade SDC tends to be uniform and sometimes random or

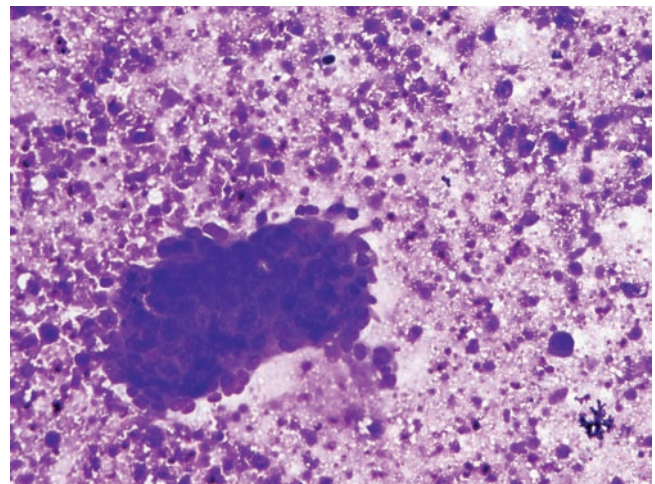


Figure 55 Salivary duct carcinoma, high-grade. Abundant necrosis is associated with the malignant cells (DQ stain, 400 $\times$).

focal in nature (144). Papillary cystadenocarcinoma (PCA) and PLGA show architectural similarities to SDC, including cystic and papillary formation (147). Because of the absence of significant atypia, these neoplasms are difficult to distinguish from low-grade SDC, but should not be confused with high-grade SDC (145,148).

Acinic Cell Carcinoma

Acinic cell carcinoma is a low-grade malignancy characterized by sheets of large cells with abundant cytoplasm. The neoplastic cells have foamy/vacuolated cytoplasm with ill-defined borders, eccentrically placed nuclei, small inconspicuous nucleoli, and lack

Table 19 Differential Cytomorphologic Features of Salivary Gland Neoplasms with Large Cells and Abundant Cytoplasm

	High-grade Salivary duct carcinoma	High-grade mucoepidermoid carcinoma	Acinic cell carcinoma	Oncocytic lesions
Architecture	Flat branching sheets and tightly cohesive clusters Occasional cribriforming and papillary formation	Tightly and loosely cohesive clusters No cribriform or papillary configuration	Large flat sheets	Large flat sheets
Cellular Features	Large monomorphic polygonal cells showing abundant eosinophilic cytoplasm with indistinct cell borders	Large atypical keratinized and nonkeratinized squamous cells. Rare mucus-producing cells	Monomorphic acinic cells with abundant foamy vacuolated cytoplasm	Large monomorphic epithelial cells with abundant dense eosinophilic cytoplasm and well-defined cytoplasmic borders
Nuclear Features	Focal/random moderate nuclear atypia, round to oval enlarged hypochromatic nuclei with prominent nucleoli	Diffuse marked nuclear pleomorphism and atypia with nuclear hyperchromasia in the squamous epithelial cells	Small eccentrically placed nuclei and inconspicuous nucleoli	Centrally placed nuclei with prominent nucleoli Nuclear/cytoplasmic ratio is low
Background	Necrosis often present	Necrosis and mucin may be present	Naked nuclei	Necrosis is absent

Source: Modified from Elsheikh Ref. 144.

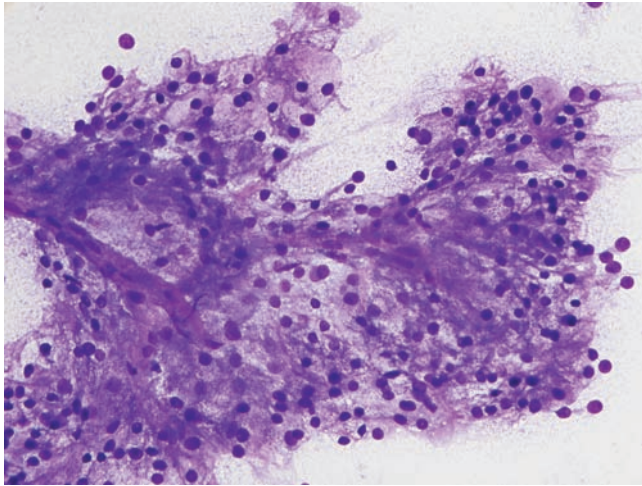


Figure 56 Acinic cell carcinoma. Flat sheets of epithelial cells, with abundant vacuolated basophilic cytoplasm and indistinct cytoplasmic borders. The nuclei are peripherally located. This cell group is traversed by thin capillaries (DQ stain, 200 $\times$).

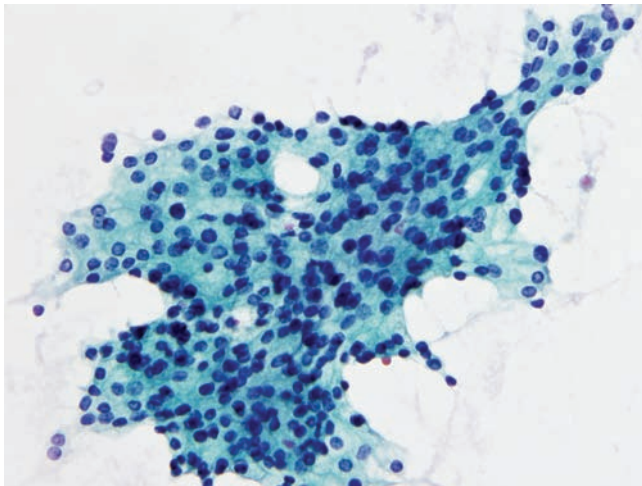


Figure 57 Acinic cell carcinoma. The neoplastic cells show no significant atypia, and round eccentrically placed nuclei with small inconspicuous nucleoli. There is suggestion of acinar configuration (Papanicolaou stain, 400 $\times$).

significant nuclear atypia or pleomorphism (Figs. 56 and 57) (149). Some cellular groups may be traversed by thin capillaries (Fig. 56). Stripped nuclei are often present in the background. Occasionally there is papillary configuration or prominent cystic component (150). A number of cases show a dense lymphocytic component, which may lead to confusion with Warthin tumor (Table 19) or other lymphoepithelial lesions (151). Because of its bland cytology, acinic cell carcinoma may be misdiagnosed as nonneoplastic acinar tissue. However, benign acinar cells have a characteristic low power rosette or clustered ball

arrangement (Fig. 36), in contrast to the flat sheets and syncytial architecture of acinic cell carcinoma.

Oncocytoma and High-Grade Oncocytic Carcinoma

Oncocytoma is characterized by large flat sheets of epithelial cells with abundant dense eosinophilic cytoplasm, well-defined cytoplasmic border, enlarged centrally placed nuclei, and prominent nucleoli. Anisonucleosis and mild atypia are not uncommon, but marked cytologic atypia, cribriforming, and necrosis are often absent.

High-grade oncocytic carcinoma may be suspected based on the presence of severe cytologic atypia, but histologic confirmation is warranted in such cases (152,153).

Warthin Tumor

Warthin tumor is almost always seen in the parotid gland, comprising approximately 5% to 10% of all parotid tumors. The aspirate has a thin watery mucoid appearance, and consists of a mixed population of lymphocytes, occasional plasma cells, and variable number of oncocytes (Fig. 58). Acinic cell carcinoma, especially if associated with a prominent lymphocytic infiltrate, may be confused with Warthin tumor. In contrast to oncocytes, acinar cells have delicate vacuolated cytoplasm and show peripherally located nuclei (Table 19); this distinction, however, can be difficult in certain situations and may require histologic confirmation. If the lymphoid component predominates in an aspirate and oncocytes are not appreciated, Warthin tumor can be misinterpreted as reactive lymphoid hyperplasia. In oncocytic-rich aspirates, it is impossible to distinguish epithelial-rich Warthin tumor from oncocytoma. Warthin tumor can also present as a

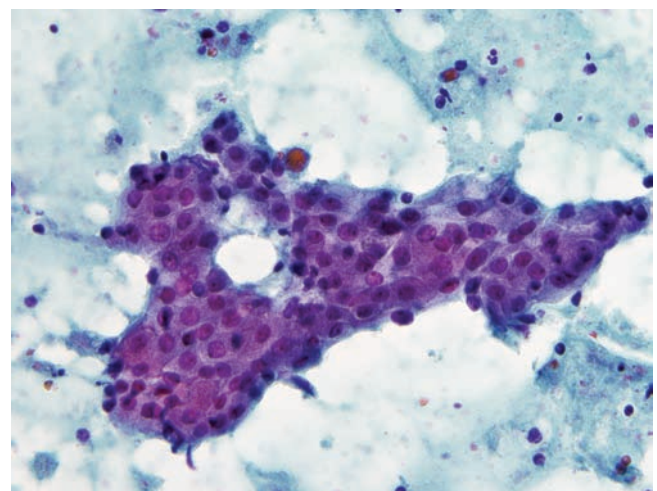


Figure 58 Warthin tumor. There is admixed population of large flat sheets of oncocytes and lymphoid cells. The epithelial cells have abundant dense eosinophilic cytoplasm, well defined cytoplasmic border, enlarged centrally placed nuclei, and prominent nucleoli (Papanicolaou stain, 600 $\times$).

predominately cystic mass with nonspecific cyst content findings, in which case it must be included in the differential diagnosis of other cystic lesions. MEC and SDC may show oncocytic features, but these changes are usually focal (142).

Metastatic Malignancies

Squamous cell carcinoma and melanoma from the head and neck make up the majority of metastases to salivary glands (154,155). Primary sites originating below the clavicle are extremely rare, but when present are usually due to metastases from lung, kidney, and breast (156). Rarely metastasis presents as the initial manifestation of disease, mimicking a primary salivary gland neoplasm. Metastatic breast ductal carcinoma and prostatic large duct carcinoma may show cytologic features identical to SDC; therefore, the possibility of metastases need to be clinically excluded before making a diagnosis of primary SDC (157). Immunocytochemical studies including estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) maybe helpful in this differential diagnosis. AR is positive in most SDC and a subset of other primary salivary gland neoplasms, but negative in breast ductal carcinoma. ER is typically negative in SDC and positive in breast carcinoma (158,159). SDC rarely expresses PR (<3% of cases) and, when positive, is seen in less than 25% of cells. Therefore, PR positivity in more than 25% of neoplastic cells favors metastatic breast carcinoma (142). Gross cystic disease fluid protein-15 (GCDFF-15), prostate-specific antigen (PSA) and prostate acid phosphatase (PAP) are not helpful markers since they are also expressed by SDC (160–163). Metastatic large cell carcinoma of the lung can mimic other primary high-grade carcinomas of the salivary gland and, if associated with cytoplasmic vacuolization and clearing, may raise the differential diagnosis of clear cell carcinoma (164). Assessment of the cytokeratin (CK) 7 and 20 immunohistochemical profiles is of limited usefulness in the distinction between primary salivary gland malignancies and metastases since most are CK7-positive/CK20-negative (165). Nonetheless, the relatively common CK20 positivity among SDC may help in distinguishing it from morphologically similar carcinomas of breast or lung. In addition, the prevalent CK7-negative/CK20-negative profile of cancers as adrenal cortical, prostatic, and RCCs can further aid in their discrimination from SDC (165). TTF-1 has been shown to be a highly specific marker for primary and metastatic lung adenocarcinoma and would be helpful in the differential diagnosis of primary high-grade carcinoma (166,167).

Radiation therapy

Radiation therapy may cause significant atypia in the lining epithelium of the salivary ducts (postirradiation atrophy and fibrosis), potentially resulting in a false-positive diagnosis of recurrent carcinoma (168). The sparsely cellular nature of the aspirate and radiation therapy changes including cytomegaly, cytoplasmic

vacuolization, nuclear smudging, and low nuclear to cytoplasmic ratios are features suggestive for therapy effect (92,136).

Clear Cell Change

Clear cell change is not uncommonly encountered in salivary gland FNAs. Neoplasms presenting with clear cell morphology are listed in Table 20. Epithelial-myoepithelial carcinoma (EMC) is regarded as a low-to intermediate-grade malignancy with propensity for local recurrence. FNA is usually of high cellularity and shows two distinct cell populations, ductal and myoepithelial (Fig. 59). The ductal cells present as tightly cohesive and three-dimensional clusters and sometimes form tubular structures. They have a basaloid appearance, i.e., small cells with scant cytoplasm, uniform round nuclei, small nucleoli and well-defined cytoplasmic borders (169–171). The myoepithelial cells are characterized by sheets and loosely cohesive groups of large cells with pale vacuolated (clear) cytoplasm, elongated nuclei, and small distinct nucleoli. Single cells and numerous naked nuclei are seen in the background.

Table 20 Salivary Gland Lesions Characterized by Clear Cells

Epithelial-myoepithelial carcinoma
Metastatic renal cell carcinoma
Hyalinizing clear cell adenocarcinoma
Acinic cell carcinoma
Mucoepidermoid carcinoma
Polymorphous low-grade adenocarcinoma
Clear cell myoepithelioma/myoepithelial carcinoma
Sebaceous adenoma/carcinoma
Clear cell oncocytoma

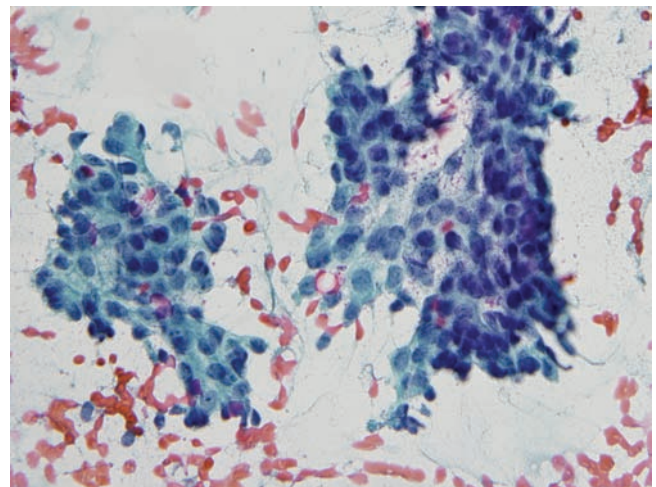


Figure 59 Epithelial-myoepithelial carcinoma. Dual populations of ductal and myoepithelial cells. The ductal cells are more cohesive, three-dimensional, and show less amount of cytoplasm. The myoepithelial cells are arranged as loosely cohesive groups of large cells with pale vacuolated (clear) cytoplasm and have round-elongated nuclei and small nucleoli (Papanicolaou stain, 400×).

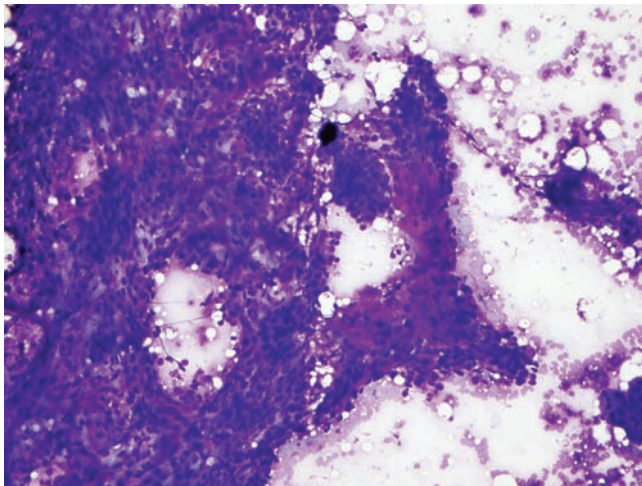


Figure 60 Epithelial-myoepithelial carcinoma. Dense acellular mesenchymal component is associated with the cell clusters (DQ stain, 200×).

Occasionally, there is predominance of the clear cells without appreciation of a basaloid cell component. Variable amount of acellular mesenchymal component, including pale blue material resembling mucin or dense stroma surrounding cell clusters, is usually present (Fig. 60) (170,171). Hyaline globules are rarely encountered and may raise the possibility of ACC. However, there is typically no significant large clear cell component in ACC. Since EMC is composed of variable mixtures of clear myoepithelial cells, basaloid cells, and hyaline stromal material, predominance of any of those components can lead to diagnostic difficulties, with many of those lesions misinterpreted as pleomorphic adenoma, ACC or low-grade malignancy (169,172). Other primary low-grade malignancies such as acinic cell carcinoma, low-grade MEC, and PLGA may have focal clear cell change, but other areas in the smears should demonstrate cytologic features characteristic of these neoplasms (111).

In clear cell-predominant aspirates, metastatic RCC must first be excluded. RCC is characterized by large cells with clear bubbly cytoplasm, distinct to wispy borders, fine vasculature, and prominent nucleoli (Fig. 32). No basaloid cells or significant number of naked nuclei are seen. Immunocytochemistry may be helpful, as RCC demonstrates positive staining for CD10 and renal cell antigen, and shows negative staining for myoepithelial markers (173,174). Also, greater nuclear atypia is usually appreciated in RCC compared with EMC. Primary (hyalinizing) clear cell adenocarcinoma of the salivary gland may show identical cytologic features to metastatic RCC. It is a low-grade malignancy with predilection for minor salivary glands. No ductal differentiation is demonstrated, and IHC is negative for myoepithelial markers (175). Myoepithelioma and myoepithelial carcinoma, clear cell types, are extremely rare and are composed of a uniform population of cells with less amount of

clear cytoplasm and no ductal differentiation (173). Variable degree of atypia is observed in myoepithelial carcinoma. Sebaceous adenoma and carcinoma are characterized by foamy vacuolated cytoplasm, no ductal cells, and negative myoepithelial markers.

In summary, it is important to recognize the broad spectrum of cytomorphologic features associated with neoplasms characterized by large cells and abundant cytoplasm; and is especially important to separate the high-grade cancers from the less aggressive neoplasms. Some aspirates are obviously malignant and show diffuse marked cytologic atypia, while others may only show focal atypia. The distinction between the various types of high-grade malignancies such as high-grade MEC, high-grade SDC, and high-grade carcinoma not otherwise specified is not critical since these patients will receive appropriate aggressive treatment. It is, however, crucial not to mistake a high-grade carcinoma for a low-grade malignancy or a benign neoplasm (144). The finding of cribriforming and necrosis with significant cytologic atypia, even if the atypia is random or focal, should raise the diagnostic possibility of high-grade SDC (144,176).

H. Salivary Gland Tumors Rich in Lymphocytes

Lymphoid cells may be associated with a variety of salivary gland lesions including benign lymphoepithelial lesion, lymphoepithelial cysts associated with AIDS, chronic sialadenitis, Warthin tumor, intraparotid lymph node hyperplasia, and malignant lymphoma (Table 21). The admixture of lymphoid cells and oncocytes is diagnostic of Warthin tumor (Fig. 58). However, careful evaluation of the lymphocytes is needed to ensure that they are reactive in nature. The presence of a monomorphic population of lymphoid cells should raise the possibility of malignant lymphoma.

Malignant Lymphoma

Primary lymphoma in salivary glands is most commonly associated with benign lymphoepithelial lesion and Sjögren's syndrome, or occasionally Warthin tumor. Malignant lymphoma can arise in intraparotid or periparotid lymph nodes. Lymphoma may also secondarily involve the salivary glands as part of a generalized disease or leukemia. Most lymphomas are B-cell NHL, and the majority of them are extranodal marginal zone lymphoma (MALT type), follicular

Table 21 Lymphoid-Rich Salivary Gland Lesions

Chronic sialadenitis
Benign lymphoepithelial lesion
Lymphoepithelial cyst
Intraparotid lymph node hyperplasia
Warthin tumor
Acinic cell carcinoma
Mucoepidermoid carcinoma
Malignant lymphoma
Lymphoepithelial carcinoma
Metastatic carcinoma

lymphoma, or DLBCL (177). Establishing a diagnosis of malignancy in large cell lymphoma is not difficult, but high-grade carcinoma, small cell carcinoma, and melanoma must be excluded. The cytologic diagnosis of low-grade lymphoma, including small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia and MALT lymphoma is most challenging as it is difficult to distinguish them from reactive lymphoid hyperplasia. Immunocytochemistry and/or flow cytometry play a pivotal role in establishing a definitive diagnosis in these cases (178). Hodgkin's lymphoma (HL) rarely involves the salivary glands, but shows a background of mixed inflammatory cells including plasma cells and eosinophils and variable number of Reed Sternberg cells and their mononuclear variants. Atypical naked single and multilobated nuclei are often present in the background. Immunocytochemical stains including CD15 (Leu-M1) and CD30 highlight the neoplastic cells.

Lymphoepithelial Carcinoma

Lymphoepithelial carcinoma is an aggressive undifferentiated malignancy characterized by mixture of lymphocytes, plasma cells, and syncytial sheets of large- to spindle-shaped cells (104). The malignant cells show marked pleomorphism and have scant to moderate amount of cytoplasm, vesicular nuclei, and prominent nucleoli (179,180). Differential diagnosis includes other high-grade malignancies such as large cell lymphoma, melanoma, and metastatic carcinoma, including nasopharyngeal carcinoma.

Lymphoid Hyperplasia and Lymphoepithelial Lesions

Lymphoid hyperplasia may be encountered in aspirates of intraparotid, periparotid, or submandibular lymph nodes that are mistaken clinically for salivary gland neoplasms. These aspirates are composed of a mixed population of lymphoid cells, including small lymphocytes, large follicular center cells, plasma cells, and tingible body macrophages. *Benign lymphoepithelial lesion (lymphoepithelial sialadenitis)* shows a similar reactive lymphoid component, but scattered tightly cohesive clusters of ductal epithelial cells (lymphoepithelial islands) will be invariably found (Fig. 61) (177). Admitting, however, in the absence of the epithelial elements, distinction from lymph node hyperplasia is not possible. Lymphoepithelial cysts and *HIV-associated cystic lymphoepithelial lesions* have prominent cystic components and show reactive lymphoid cells admixed with mucoid debris and macrophages (181,182). Metaplastic squamous and glandular cells may be found, which can raise the possibility of cystic low-grade MEC.

Chronic sialadenitis may show a prominent reactive-lymphoid cell population admixed with ductal cells. The sparse cellularity of the specimen, in addition to the presence of occasional fibroblasts, neutrophils and benign acinar cells favor a diagnosis of chronic sialadenitis (103,105). Finally, low-grade malignancies such as acinic cell carcinoma and MEC may be associated with a rich lymphoid infiltrate, resulting in a false-negative diagnosis of reactive lymphoid hyperplasia. Hence, it is crucial to carefully

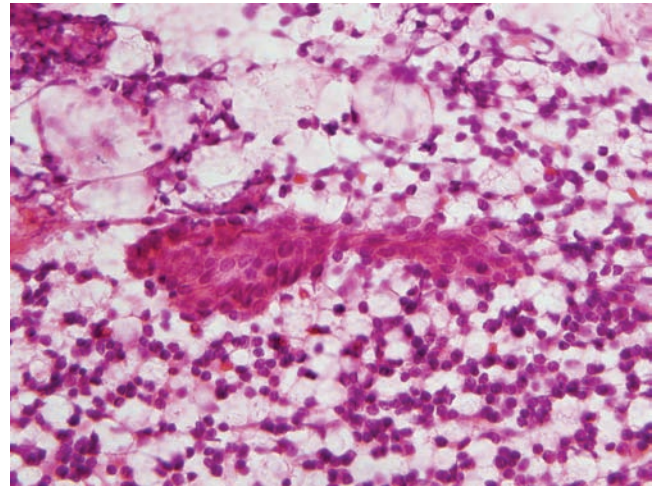


Figure 61 Benign lymphoepithelial lesion (lymphoepithelial sialadenitis). Lymphoepithelial islands, when present, are characteristic. They consist of tightly cohesive clusters of ductal epithelial cells intermingled with reactive lymphoid cells (H&E stain, 200 $\times$).

examine lymphoid-rich specimens for evidence of low-grade malignancy hiding in the background.

I. Pleomorphic Adenoma and its Variable Cytologic Appearances

Pleomorphic adenoma (PA) is the most common neoplasm of the salivary glands, accounting for approximately 75% of neoplasms, with a peak age of 30 to 40 years (183,184). It is characterized by admixture of cellular (ductal and myoepithelial cells) and mesenchymal components (Fig. 62). The mesenchymal component may be myxoid or chondroid and is usually admixed with spindle myoepithelial cells. The myxoid mesenchymal component stains poorly with Papanicolaou stain, appearing gray or pale green; but is better highlighted by DQ stain as dark purple material with a fibrillary appearance (Fig. 63) (123). The stromal material is usually the most characteristic feature of PA, but other neoplasms may also be rich in extracellular stroma (Table 14) (185,186). Recognizing the intimate admixture of the cellular and mesenchymal elements, on FNA, is what establishes the diagnosis of PA (183,184).

PA is notorious for mimicking the cytologic appearance of other tumors, especially low-grade malignancies. Therefore, PA should be considered in the differential diagnosis in the lesions listed in Table 22. Although most cases of PA show classic cytologic features of admixed mesenchymal, ductal, and myoepithelial elements, problems in the diagnosis may be encountered if there is a predominance of any one of these elements (136,187). If the mesenchymal myxoid stroma, for instance, predominates in an aspirate it can be misinterpreted as mucin, causing PA to be mistaken for cyst fluid or low-grade MEC. In

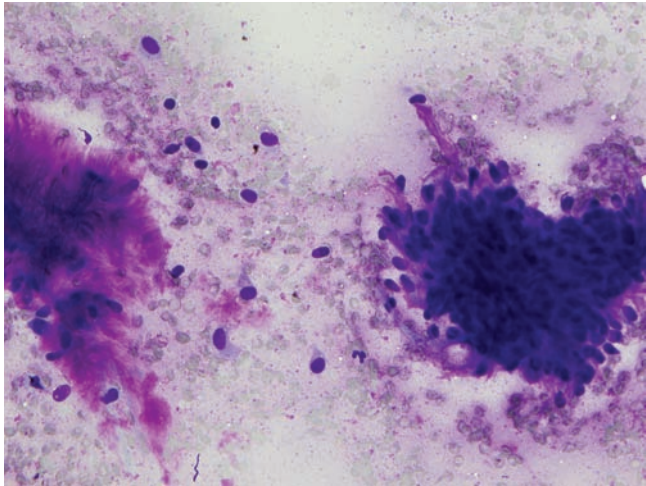


Figure 62 Pleomorphic adenoma is characterized by admixture of cellular (ductal and myoepithelial cells) and mesenchymal components. The ductal cells present as cohesive groups. Myoepithelial cells, present in the background, have a plasmacytoid appearance. The mesenchymal component stains dark purple and has cells embedded in it (DQ stain, 200 $\times$).

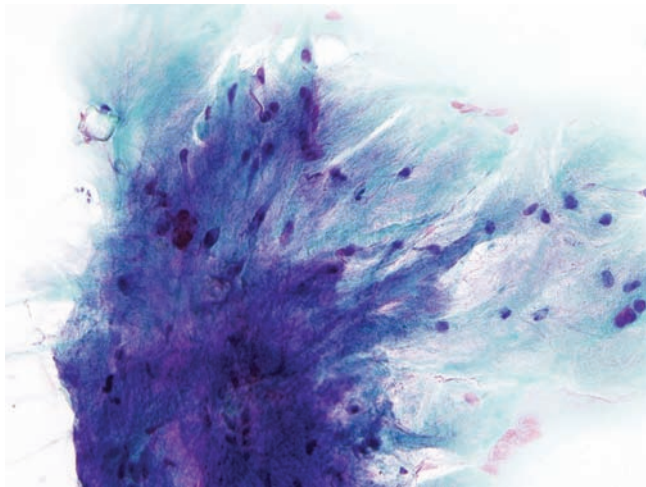


Figure 63 Pleomorphic adenoma. This myxoid mesenchymal component has a fibrillary appearance, and shows intimately admixed spindle myoepithelial cells (Papanicolaou stain, x 400).

cellular PA, where the epithelial/myoepithelial cells predominate, other salivary gland neoplasms such as basal cell adenoma, ACC, and low-grade malignancies may be suspected (123,136,187). Because of the increased rate of false-positive and false-negative diagnoses associated with these cellular lesions, some authors have recommended for highly cellular lesions lacking stroma to be classified as “salivary gland neoplasm, not otherwise specified” (108).

Table 22 Neoplasms That Have Overlapping Cytologic Features with Pleomorphic Adenoma

Basal cell adenoma
Adenoid cystic carcinoma
Spindle cell tumors
Oncocytoma, Warthin tumor
Acinic cell carcinoma
Low-grade mucoepidermoid carcinoma
Myoepithelioma
Epithelial-myoepithelial carcinoma
Polymorphous low-grade adenocarcinoma
Low-grade salivary duct carcinoma
Carcinoma ex pleomorphic adenoma

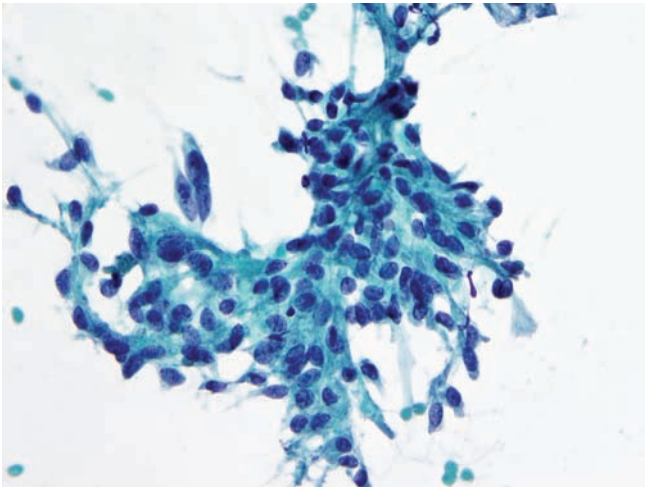


Figure 64 Pleomorphic adenoma. The neoplastic cells have moderate amount of cytoplasm, round to oval nuclei, finely granular chromatin, and lack distinct nucleoli. Focal atypia is seen (at 10:00), which is acceptable in pleomorphic adenoma (Papanicolaou stain, 400 $\times$).

Cellular PA

Cellular PA is characterized by the presence of loosely cohesive branching and arborizing sheets of intermediate-sized cells with indistinct (fuzzy) community borders (Fig. 64). There is a haphazard cellular arrangement with occasional spindling (123). The neoplastic cells have moderate amount of cytoplasm, oval to round nuclei, finely granular chromatin, and lack distinct nucleoli. Typically, the background shows singly scattered cells with plasmacytoid appearance (myoepithelial cells) (188). Mesenchymal elements may be scant or absent. Basaloid neoplasms are the most difficult lesions to distinguish cytologically from cellular PA, an experience shared by several authors (123,187). *Basal cell adenoma* is characterized by tightly cohesive clusters of small basaloid cells, and many naked nuclei in the background. Cellular PA, in contrast, has intermediate-sized cells with moderate amount of cytoplasm, and plasmacytoid cells in the background (Table 23). ACC is also considered in the differential diagnosis, as PA may

Table 23 Major Differential Diagnostic Considerations of Cellular Pleomorphic Adenoma

	Cellular pleomorphic adenoma	Basal cell adenoma	Adenoid cystic carcinoma	Low-grade mucoepidermoid carcinoma
Architecture	Broad, loosely cohesive sheets Indistinct community borders May have empty pseudocysts	Tightly cohesive clusters Smooth community borders	Broad sheets Microcysts contain large hyaline globules	Loosely cohesive sheets and few 3-D clusters
Cellular features	Intermediate-sized cells Moderate cytoplasm Haphazard arrangement	Small-sized cells Scant cytoplasm	Small cells Scant cytoplasm	Intermediate-sized cells Monomorphic population
Nuclear features	Round to oval nuclei Finely granular chromatin No nucleoli	Round to oval nuclei Finely granular chromatin No nucleoli	Round to oval nuclei Coarse chromatin Occasional nucleoli	Round to oval nuclei Finely granular chromatin Small nucleoli
Background Extracellular matrix	Plasmacytoid cells Fibrillary myxoid or chondroid substance admixed with spindle cells	Naked nuclei Amorphous, homogenous, stromal material surrounding neoplastic cells	Naked nuclei Dense hyaline globules surrounded by neoplastic cells	Single cells Stringy mucin, admixed with macrophages

Source: Modified from Ref. 123.

focally show pseudocystic spaces or contain small hyaline globules. This is a potential diagnostic pitfall that has been described in several reports (123,187,189,190). Careful examination, however, reveals that these spaces are empty and do not contain the large hyaline globules characteristic of ACC. In addition, the globules associated with PA are often small and focal in nature (Fig. 65), in contrast to the numerous large and variably sized globules associated with ACC (Figs. 46 and 47) (111,113,191). Furthermore, the neoplastic cells of PA have more abundant cytoplasm, compared to the basaloid cell appearance of ACC (Table 23). It is important to distinguish cellular PA from basaloid neoplasms especially ACC, since the latter is an aggressive malignancy characterized by recurrences and late metastasis to lungs and bone. Rarely, ACC may arise in PA, in which case the cytologic features of both neoplasms are present (192).

Spindle Cell Lesions

Cellular PA may have a predominant spindle cell appearance, which could lead to confusion with soft tissue spindle cell neoplasms (123). Cytologically, the specimen is composed of cohesive clusters of spindle cells with overlapping nuclei and crowding (Fig. 66). Careful search of the background for mesenchymal elements is needed in such cases as this may be the only clue to the diagnosis of PA. Otherwise, it is difficult to differentiate spindle PA from other spindle cell tumors such as nerve sheath tumor, leiomyoma, myoepithelioma, and low-grade sarcoma (Table 24). Occasionally inflammatory conditions, such as granulomatous sialadenitis, show a spindle cell appearance, but recognition of epithelioid histiocytes and mixed inflammatory background should secure the diagnosis. Malignant neoplasms such as metastatic spindle cell melanoma and high-grade sarcoma have

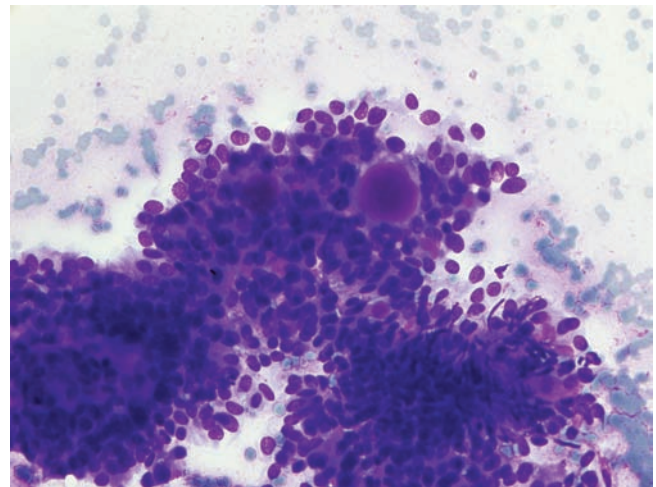


Figure 65 Pleomorphic adenoma. Rare hyaline globules may be encountered. These globules are small, uniform in size, and have irregular outer contours (DQ stain, 200×).

also been reported (193). Histologic confirmation is warranted in newly diagnosed spindle lesions.

Hyaline PA

Plasmacytoid variant of PA (hyaline PA) is characterized by sheets, clusters, and singly scattered plasmacytoid appearing cells. The cells have abundant dense/glassy cytoplasm with well-defined border, round to oval eccentrically placed nuclei, and inconspicuous nucleoli (Fig. 67). These cells most likely represent modified myoepithelial cells (194,195). Differential diagnosis includes other neoplasms with abundant cytoplasm and no significant atypia, such as acinic cell carcinoma and oncocytic tumors (Table 22).

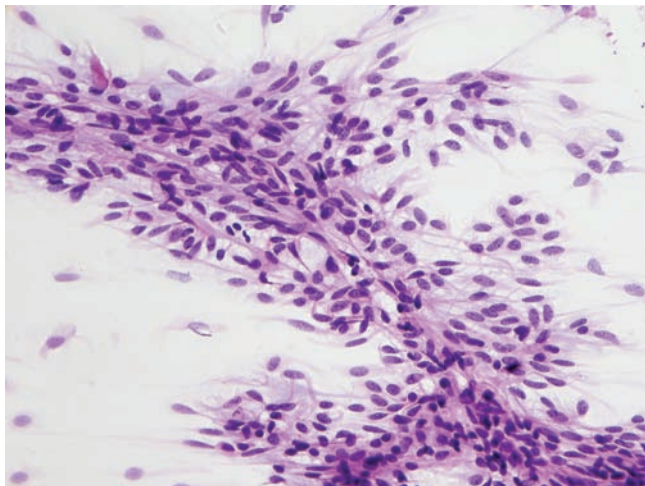


Figure 66 Spindle pleomorphic adenoma/myoepithelioma, showing cohesive clusters of spindle cells with overlapping nuclei and crowding and no significant atypia (Papanicolaou stain, 400×).

Table 24 Differential Diagnosis of Spindle Cell Neoplasms
Cellular pleomorphic adenoma
Myoepithelioma
Nerve sheath tumor
Leiomyoma
Sarcoma, low grade and high grade
Nodular fasciitis
Granulomatous sialadenitis
Malignant melanoma

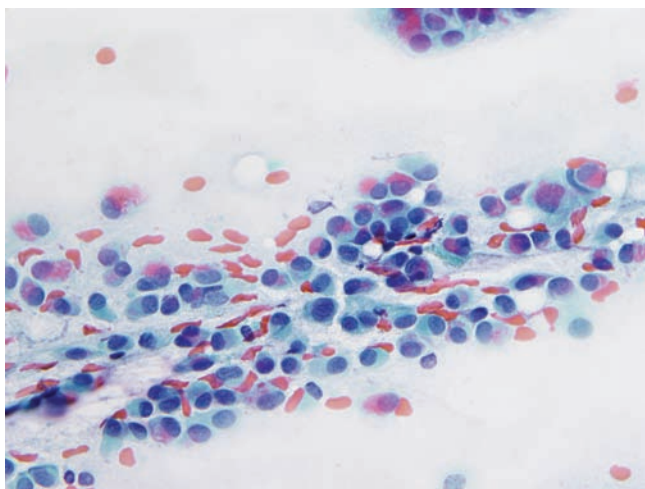


Figure 67 Hyaline (plasmacytoid) pleomorphic adenoma/myoepithelioma. The specimen consisted predominately of plasmacytoid appearing cells having abundant dense/glassy cytoplasm, with well-defined border, round to oval eccentrically placed nuclei, and inconspicuous nucleoli (Papanicolaou stain, 600×).

Acinic cell carcinoma has eccentrically placed nuclei similar to hyaline PA, but the cytoplasm has a foamy granular quality with indistinct borders. Oncocytic tumors, such as Warthin tumor and oncocytoma, have dense eosinophilic cytoplasm similar to PA, but the nuclei are centrally placed and show prominent nucleoli (123). Differential diagnosis also includes plasmacytoma, which is distinguished by nuclei showing characteristic clumpy cartwheel chromatin, perinuclear hoff, and plasma cell markers (CD79a, CD138, kappa/lambda light chain).

Myoepithelioma and Myoepithelial Carcinoma

Myoepithelioma is a rare benign neoplasm that is regarded as a monomorphic variant of PA. It is histologically characterized by proliferation of myoepithelial cells and scant-to-absent ductal elements (110). Spindle, plasmacytoid, epithelioid, and clear cell variants are recognized (Figs. 66 and 67). *Myoepithelial carcinoma (malignant myoepithelioma)* is characterized by an infiltrative destructive growth, increased mitotic activity and pleomorphism (196,197). However, the diagnostic finding that distinguishes myoepithelial carcinoma from benign myoepithelioma is the unequivocal infiltrative destructive growth of malignancy (110). Therefore, in the absence of cytologic atypia, FNA cannot distinguish cellular PA and myoepithelioma from myoepithelial carcinoma (123).

PA vs. Low Grade Malignancies

Separating cellular PA from low-grade malignancies, such as low-grade MEC, EMC, and PLGA, can be quite challenging. In low-grade MEC, the predominance of intermediate cells with bland cytology can be easily mistaken for the epithelial component of PA (108). Also, the mucinous material in the background may be misinterpreted as the myxoid stromal component of PA (128). Helpful distinguishing features are the stringy nature of mucin admixed with macrophages in MEC versus the fibrillary myxoid stroma admixed with spindle cells in PA. Additional differentiating features are listed in Table 23. Low-grade SDC has been misdiagnosed as PA in one study and PLGA may be difficult to tell apart from cellular PA, but this latter diagnosis should not be considered in aspirations of the parotid or submandibular glands, since PLGA is seen almost exclusively in minor salivary glands (particularly the palate) (145,148). The bland nuclear features of low-grade malignancies combined with prominent metachromatic desmoplastic stroma have resulted in these few reported cases of false-negative diagnoses. The presence of prominent nucleoli, lack of background plasmacytoid myoepithelial cells, and absence of intimate admixture of myoepithelial cells and fibrillary extracellular stroma, however, should prevent a misclassification of PA in most cases (123). Squamous and mucinous metaplasia have been described in PA, but this finding is often focal and should not raise the possibility of MEC. EMC is characterized by dual populations of basaloid (ductal) and

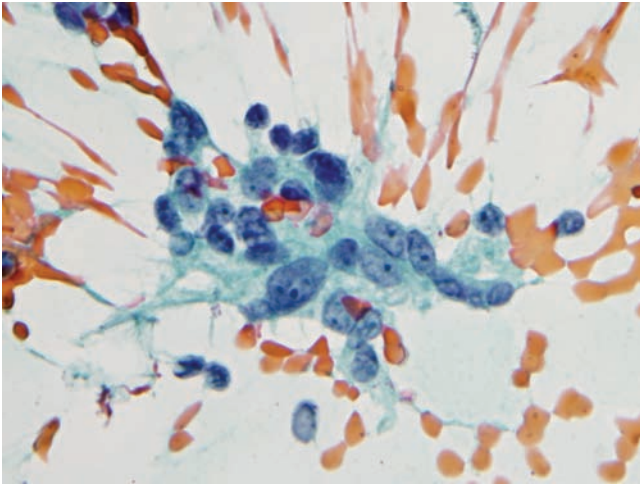


Figure 68 Carcinoma ex pleomorphic adenoma. There is severe cytologic atypia and nuclear pleomorphism present throughout the smears. Focally, there are cytologic features of pleomorphic adenoma. This degree of atypia, however, is beyond what is accepted for pleomorphic adenoma (Papanicolaou stain, 600 $\times$).

clear (myoepithelial) cells admixed with extracellular hyaline material. The prominence of clear cell component, numerous naked nuclei, and acellular quality of the extracellular stroma help in separating it from cellular PA.

Finally, cytologic atypia may be seen in up to 20% of PA and accounts for many of the problems leading to false-positive diagnoses (191). Focal mild atypia is acceptable in PA and should not raise concerns for malignancy. This atypia may manifest as scattered large cells with round to oval nuclei and prominent nucleoli in an otherwise classic presentation of PA (Fig. 64) (104). Severe cytologic atypia, however, should raise the possibility of carcinoma ex pleomorphic adenoma (Fig. 68). Typically, the malignancy associated with carcinoma ex pleomorphic adenoma is poorly differentiated, and aspirates almost invariably contain numerous anaplastic malignant cells without cytologic evidence of PA (187). A definitive diagnosis of carcinoma, therefore, should not be rendered in the absence of overt malignant cytologic features, as most cases of PA-associated atypia are benign on follow-up. Low-grade malignancies arising in PA have been rarely reported (198).

J. Summary of Salivary Gland FNA

Preoperative FNA of salivary gland tumors is clinically useful and is especially helpful in distinguishing neoplastic from nonneoplastic lesions. In most cases, it is not critical to distinguish between benign neoplasms and low-grade malignancies, since patients with either type of neoplasm will be managed conservatively. It is very important, however, to separate high-grade malignancies from benign neoplasms and

low-grade cancers. Because of the challenging nature of salivary gland FNAs, there is a potential significant false-positive and false-negative rate, which should improve with experience. In our discussion, we have stressed the major difficulties and limitations associated with FNA cytology and provided a morphologic diagnostic approach to the interpretation of such specimens. This approach emphasized the differential diagnostic possibilities and stressed the importance of well-defined cytologic criteria. If established diagnostic criteria are present and strictly observed, the great majority of nonneoplastic lesions and common variants of benign and malignant neoplasms can be diagnosed with a high level of accuracy (89). However, there will remain a subset of problematic cases where a specific diagnosis is not possible. Under these circumstances, the clinician is best served with an appropriate differential diagnosis, relating the uncertainty of the interpretation and the recommendation for surgical pathology examination to help establish a more definitive diagnosis.

IV. LYMPH NODES

A. Introduction

Fine needle aspiration biopsy (FNAB) is a well-accepted diagnostic test of choice for the assessment of cervical and supraclavicular lymphadenopathy in both adult and pediatric patients. In the majority of cases, FNAB can reliably distinguish between benign/reactive and malignant processes. In most cases, results of FNAB can provide adequate information to accurately guide patient management with either simple observation, antimicrobial therapy for infectious processes, chemotherapy and radiation therapy for malignancies, or the need for additional tissue in the form of core biopsies or excisional biopsy of the lymph node. The technique is well accepted among both oncologists and pathologists for the diagnosis of metastatic malignancies and the documentation of lymphoma recurrences. Workup of metastatic neoplasms has shown both high sensitivity (91–98%) and high specificity (95–99%) with an overall accuracy rate of 94% to 97% (199–203). However, its role for the primary diagnosis of lymphomas has remained controversial (204). The recent changes in the WHO classification of lymphomas has placed more emphasis on cytomorphologic rather than on architectural features allowing for a more expanded role of FNAB in the primary workup of NHLs (205). The evaluation of HL still remains problematic; and while FNAB may suggest the diagnosis based on cytomorphologic features, it is often still necessary to obtain a tissue biopsy for a definitive diagnosis (178,206). In the workup of lymphadenopathy, a combined approach correlating the cytomorphologic features with results from ancillary tests such as immunohistochemistry, flow cytometry, and molecular diagnostics [fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR)] yield more accurate results than any single modality alone (207–210).

B. Clinical Considerations

The workup of lymphadenopathy in the head and neck region requires close clinicopathologic correlation to arrive at an appropriate differential diagnosis, including patient age, prior medical history, clinical symptoms including anatomic location, and chronicity. The age of the patient is especially useful as the etiology of lymphadenopathy is vastly different in children compared with adults.

In the pediatric age group, FNAB is especially advantageous since tissue biopsy requires general anesthesia and the risk of potential morbidity, including scarring and cranial nerve injury. In this age group, the vast majority of cervical lymphadenopathy is due to reactive lymphoid proliferations, most of which are associated with infectious etiologies. Although much less likely, the possibility of a metastatic neoplasm must always be ruled out. The most commonly metastasizing pediatric neoplasms include small, round blue-cell neoplasms (neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, Wilms' tumor) and osteosarcoma that can be diagnosed by FNAB (211). Malignant lymphomas of childhood include high-grade lymphoblastic lymphoma, small non-cleaved cell (Burkitt's and non-Burkitt's) lymphoma, and intermediate-grade large cell lymphoma. In the adolescents and young adults, metastases from germ cell tumors, nasopharyngeal carcinomas, as well as Hodgkin lymphoma (HL) and NHL are most commonly seen (212).

In adults, especially after the age of 40 years, lymphadenopathy in the head and neck region due to a malignancy becomes the primary diagnostic consideration. A clinical history of alcohol and tobacco usage increases the likelihood of metastatic disease. FNAB is highly accurate in the workup of patients with a potential of metastatic squamous cell carcinoma and is, therefore, a widely used first-line diagnostic technique accepted by head and neck surgeons and oncologists (213). In patients with a past history of malignancy, FNAB is especially useful for accurately establishing metastatic disease. A history of an HIV infection raises the differential diagnosis of reactive lymphadenopathies as well as malignant lymphoma. Immunosuppression increases the possibility of opportunistic infections, including *mycobacterium avium-intracellulare* (MAI) and fungal infections such as cryptococcus and histoplasma. Infectious processes can be easily recognized by FNAB and additional material can be obtained for culture.

C. Diagnostic Approach

An on-site cytopathologist for immediate interpretation and appropriate triage of the aspirated specimen greatly increases the diagnostic accuracy of FNAB. Appropriate triage also allows for a cost-effective workup of lymphadenopathy of unknown origin. Immediate evaluation of the aspirate can help categorize lesions as inflammatory lesions or as an epithelial, primary lymphoid, or nonlymphoid nonepithelial neoplasm. On the basis of this broad initial subcategorization, additional

dedicated needle passes can be performed for cell block preparation to perform immunohistochemistry or placed in transport media for flow cytometry, electron microscopy, and molecular diagnostic studies.

As with the evaluation of FNAB smears from other organs, the use of both low- and high-power magnification is recommended. Evaluation of the predominant pattern of cell dispersion, cell size, and background elements provides important diagnostic clues as to the etiology (Tables 25–30). The presence of cohesive cell clusters raises the possibility of metastatic carcinoma, certain HLs, NHLs, and granulomatous inflammation, and even nonneoplastic lymphohistiocytic aggregates. Singly dispersed cells raise the differential diagnostic consideration of malignant melanoma, primary lymphoid lesions, and poorly differentiated metastatic carcinomas. Monomorphic singly dispersed cells are most often seen in malignant

Table 25 Lymph Node Aspirates with a Large-Cell Pattern

Metastatic carcinoma
Malignant melanoma
Germ cell tumors
Anaplastic large cell lymphoma

Table 26 Lymph Node Aspirates with a Small-Cell Pattern

Reactive hyperplasias
Small lymphocytic lymphoma/chronic lymphocytic leukemia
Mantle cell lymphoma
Marginal-zone lymphoma
Follicular lymphoma
Burkitt's lymphoma
Small cell carcinoma
Sarcoma (rhabdomyosarcoma, Ewing's/PNET, neuroblastoma)
Malignant melanoma
Lymphocyte-rich classical Hodgkin's lymphoma

Table 27 Lymph Node Aspirates with a Squamous Pattern

Metastatic squamous cell carcinoma
Benign inclusion cysts
Branchial cleft cysts
Germ cell tumors
Mucoepidermoid carcinoma
Malignant melanoma, spindle variant

Table 28 Lymph Node Aspirates with Biphasic Pattern (Small and Large Cells)

Reactive hyperplasias
Follicular lymphomas
Partial involvement of a lymph node by lymphoma
Lymphocyte-rich classical Hodgkin's lymphoma
Classical Hodgkin's lymphoma
T-cell-rich diffuse large B-cell lymphoma
Malignant melanoma
Metastatic carcinoma (malignant mixed müllerian tumors)
Germ cell tumors
Sarcomas (malignant fibrous histiocytoma, synovial sarcoma)
Cat-scratch disease
Toxoplasmosis

Table 29 Lymph Node Aspirates with a Neutrophil Rich Pattern

Abscess
Inflamed inclusion cyst
Cat-scratch disease
Metastatic carcinoma (squamous cell carcinoma)
Anaplastic large cell lymphoma

Table 30 Lymph Node Aspirates with a Histiocyte-Rich Pattern

Infectious granulomas
Sarcoidosis
Toxoplasmosis
Cat-scratch disease
Kikuchi syndrome
Rosai-Dorfmann disease
Langerhans' cell histiocytosis
Germ cell tumors

lymphomas compared with reactive lymphoid lesions, which are polymorphic in appearance. The background should be evaluated for necrosis, pigment, and lymphoglandular bodies. The latter are an important clue indicative of a lymphoid cell population and are characterized as pale, basophilic rounded structures between 2 and 7 μm in size and representing fragments of lymphocyte cytoplasm (Fig. 69). Lymphoglandular bodies are seen in both reactive and neoplastic lymphoid proliferations, but their presence is a helpful clue to differentiate lymphoid proliferations from other small round-cell malignancies such as rhabdomyosarcoma, Ewing's sarcoma, and undifferentiated carcinomas. It must be kept in mind that partial involvement of a lymph node by metastatic carcinoma may yield

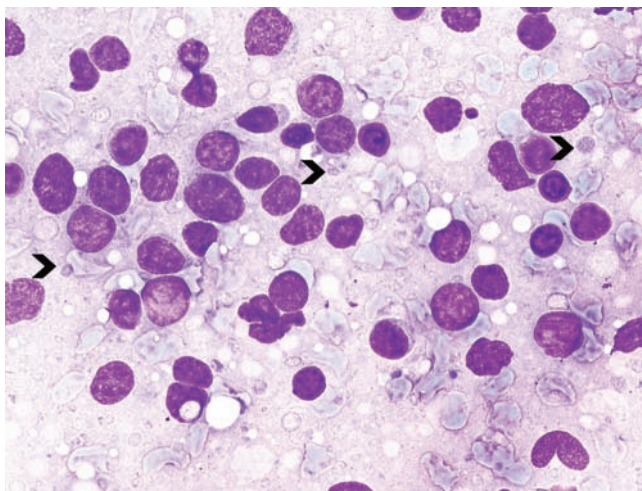


Figure 69 Lymphoglandular bodies (arrowheads) are pale, basophilic rounded structures sized between 2 and 7 μm and representing fragments of lymphocyte cytoplasm. They are seen in both reactive and neoplastic lymphoid proliferations (DQ stain, 400 $\times$).

large numbers of lymphoglandular bodies arising from the residual lymphoid cells.

D. FNA of Non-Hodgkin Lymphomas

Because of the extensive clinical overlap between non-neoplastic reactions such as reactive lymphoid hyperplasia, lymphoma, and carcinoma, the use of FNA remains a controversial topic, especially for a primary lymphoma diagnosis (204). Lymph node FNA has a modest to high sensitivity (66–100%, average >80%), high specificity (58–100%, average >90%), and high diagnostic accuracy (50–100%, average >85%) for NHLs (199,204,207,208,214–219). In comparison, FNA of HL has a lower sensitivity (48–86%), but a similar high specificity rate (98–100%) (201,220–222). The use of ancillary testing with flow cytometry, immunohistochemistry, and molecular techniques has led to a higher sensitivity and specificity and higher accuracy for the diagnosis of lymphoid neoplasms by FNAB. Additionally, the recent acceptance of the WHO classification scheme has allowed a more widespread use of FNAB, since it places less importance on architecture and more emphasis on cytomorphology in combination with immunophenotype, genotype, and clinical characteristics (204,205). Up to 85% of lymphomas may be accurately classified by morphology alone, but total reliance on morphology can lead to misdiagnoses, such as a large cell lymphoma misdiagnosed as a poorly differentiated carcinoma, HL mistaken for granulomatous inflammation or a viral infection and finally, or an overdiagnosis of a monomorphic lymphoid population in a reactive hyperplasia as a small cell lymphoma (223).

E. Ancillary Studies

Cell Block and Core Needle Biopsy

Cell block and core needle biopsy (CNB) are important diagnostic adjuncts in lymph node FNAB. The application of IHC in paraffin embedded cell block preparations and/or CNBs is essential for an accurate lymphoma diagnosis (219). The use of CD20 and CD3 immunostains can group most processes into broad categories of B-cell dominance, T-cell dominance, or a mixed B-cell and T-cell infiltrate. Additional more specific antibody panels can then be applied to B-cell and T-cell processes for more specific classification. In situ hybridization techniques for lambda and kappa light chains have been successful in establishing clonality, and show less nonspecific background staining compared with conventional immunohistochemistry (224). In patients at high surgical risk, CNB or a cell block is particularly useful for evaluating lymphadenopathy. In these cases, the tissue preparation can provide architectural features important in the diagnosis of lymphoma. The failure rate of core biopsy ranges from 14% to 58% according to various studies (225–228).

Flow Cytometry

Flow cytometry is critically important in lymph node FNAB and has the distinct advantage of evaluating a

large population of cells. Flow cytometry allows detection of small subpopulations of monoclonal cells and detection of low intensity expression of some markers that can be missed by IHC alone (210,229). Several studies have shown that the addition of flow cytometry increases the sensitivity and accuracy of lymph node FNAB, especially in demonstrating B-cell clonality by kappa and lambda light chain expression, a information that is vital for establishing a B-cell malignant lymphoma (178,207,208, 210,230,231). Nearly all small cell lymphomas show clonality in FNAB specimens, especially in small lymphocytic lymphoma (SLL) follicular lymphoma, and mantle cell lymphoma (MCL). The combination of CD19 with other antigens such as CD5, CD10, CD23, and FMC7 allows phenotypic definition of more specific lymphoma subtypes of B-cell origin (231). In comparison, less than 50% of large B-cell lymphomas show a monoclonal population by flow cytometry (217,230). This may be due to a high fragility and lower viability of large lymphoma cells, a lack of surface immunoglobulin light chain expression, extensive necrosis, and fibrosis.

Flow cytometry can also be limited by low cellularity of the sample, as well as occasional problems with nonspecific staining (217). Therefore, it must be interpreted in the context of the cytomorphologic findings from FNAB to avoid pitfalls such as coexisting neoplastic and reactive cells in the specimen. It is important to recognize that the lack of identification of a monoclonal population does not rule out a malignant lymphoma. In clinically suspicious cases, additional sampling or tissue biopsy should be recommended. HL cannot be reliably diagnosed by flow cytometry.

FISH and PCR

FISH and PCR studies have shown that sufficient material can be obtained with FNAB for analysis (232). FISH analysis can be performed on air-dried cytologic smears, cytopspins prepared from cell suspensions, or destained archival cytologic smears. More consistent results are obtained from cytopspin preparations as the cell suspension is concentrated and evenly distributed on the slide. FISH studies for cyclin-D1 and Bcl-2 can be useful for confirming mantle cell lymphoma (MCL) and follicular lymphoma, respectively (232,233). PCR can reliably detect immunoglobulin gene rearrangement, Bcl-2 gene rearrangement, and T-cell receptor gene rearrangement from material obtained via FNAB. Other new technologies recently applied to FNA include real-time PCR, automated DNA sequencing that aids in detecting any false-positives, and gene expression profiling to aid in subtyping lymphomas (234–236).

F. FNAB of Selected Non-Hodgkin Lymphomas

Lymphoblastic Lymphoma

Lymphoblastic lymphoma (Table 31) is an aggressive, rapidly growing neoplasm that comprises up to 50% of lymphomas of childhood, most often affecting

Table 31 Key Diagnostic Features—Lymphoblastic Lymphoma

Cellular smears with dissociative cell pattern
Monotonous lymphoblasts with minimal cell variation (2 times size of mature lymphocytes)
Regular nuclei with minimal membrane convolutions; indistinct nucleoli
Scant cytoplasm with or without minute vacuoles

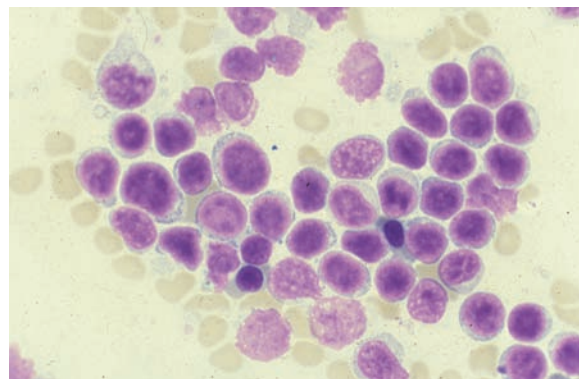


Figure 70 Aspirates from lymphoblastic lymphoma are cellular and composed of a dispersed monomorphic population of small to intermediate-sized lymphoblasts (DQ stain, 400×).

adolescent males. The anterior mediastinum is the most common location (50–80%) although, many patients have supraclavicular or cervical lymphadenopathy with most showing involvement of multiple lymph nodes. FNAB had a high diagnostic accuracy for this entity. Smears are highly cellular, with a monotonous lymphoid cell population composed of medium-sized cells with a blast morphology, round nuclei, finely granular chromatin, inconspicuous nucleoli, and scant cytoplasm (Fig. 70). Individual cell necrosis may be seen and tingible body macrophages may be numerous, imparting a “starry sky” appearance typical of an aggressive lymphoma. Mitotic activity is brisk. Phenotypically, the majority are of T-cell lineage, characterized by surface and/or cytoplasmic expression of CD3, other T-cell lineage markers, and TdT. There is often co-expression of CD4 and CD8, with some cases expressing CD10. Myeloid antigens such as CD13 and CD33 are often present and CD45 may be absent. Molecular testing demonstrates T-cell receptor gene rearrangements in approximately one-third of lymphoblastic lymphomas. Other differential considerations include Burkitt’s lymphoma, the blastoid variant of MCL, acute myeloid leukemia/chloroma, and other high-grade malignancies, including metastatic carcinomas and sarcomas. Differentiating lymphoblastic lymphoma from small cell carcinoma often requires immunostaining for cytokeratins and neuroendocrine markers.

Burkitt’s Lymphoma

Burkitt’s lymphoma (Table 32) is a highly aggressive undifferentiated lymphoma closely associated with

Table 32 Key Diagnostic Features—Burkitt's Lymphoma

Highly cellular smears with dispersed cell pattern
Monomorphic cell population; cells 2–3 times size of mature lymphocyte
Basophilic cytoplasm with many lipid filled vacuoles
Nuclei with coarse granular chromatin and 1–4 nucleoli
Cell necrosis imparting a “dirty” background
Scattered tingle-body macrophages mimicking “starry sky” pattern

the Epstein-Barr virus (EBV) that is a potentially curable neoplasm with a distinct chemotherapeutic regimen. Cervical lymph node presentation is seen in only a small percentage of patients. FNAB smears from Burkitt's lymphoma are highly cellular with a uniform population of intermediate-sized cells with round nuclei, coarse chromatin, and prominent nucleoli that are usually multiple. Characteristic peripheral cytoplasmic vacuoles are an important diagnostic clue for Burkitt's lymphoma and are almost always present on Romanowsky-type stains (Fig. 71). The background contains numerous tingible body macrophages imparting a starry-sky appearance, mitoses, and apoptotic cells, indicating a high proliferation rate (Fig. 72) (178). Immunophenotypically, Burkitt's lymphoma shows a B-cell phenotype with monoclonal surface immunoglobulin light chain and CD10 expression. This phenotype is indistinguishable from a follicular lymphoma and, therefore, differentiation between the two lymphomas is based on the cytomorphic features. Burkitt's lymphoma demonstrates a mature B-cell phenotype without expression of TdT and CD34, which separates it from lymphoblastic lymphoma. Genetically, all Burkitt's lymphoma harbors a rearrangement of the c-myc proto-oncogene on chromosome 8. The most common translocation is t(8;14), which occurs in 80% and involves the immunoglobulin heavy chain gene on chromosome 14. The less common types include t(2;8) and t(8;22). These translocations are demonstrable by FISH (237). The c-myc rearrangement can also be seen in other lymphomas such as diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma, and multiple myeloma. Therefore, diagnosis of Burkitt's lymphoma requires correlation of the clinical, morphologic, immunophenotypic, and cytogenetic findings.

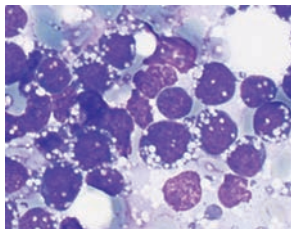


Figure 71 In Burkitt's lymphoma, uniform intermediate-sized malignant lymphoid cells are seen with numerous small, round cytoplasmic vacuoles (DQ stain; oil magnification, 600 $\times$).

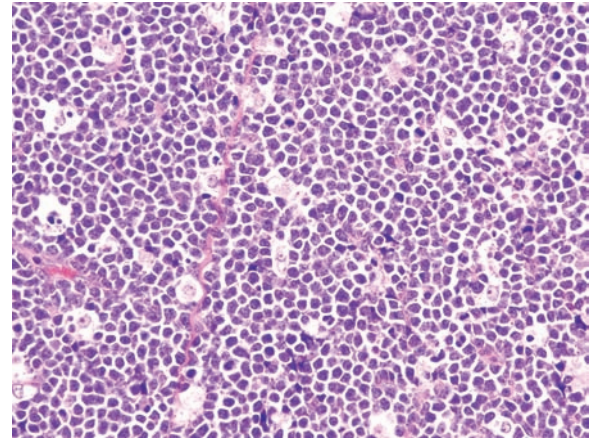


Figure 72 A core needle biopsy from Burkitt's lymphoma contains numerous background tingible body macrophages imparting a “starry sky” appearance (H&E stain; magnification, 200 $\times$).

Diffuse Large B-Cell Lymphoma

DLBCL comprises 30% to 40% of adult NHL, can occur at any age, and is an aggressive but potentially curable neoplasm. FNAB smears from DLBCL contain a monomorphic population of large cells with vesicular-cleaved or noncleaved nuclei that are two to three times the size of a reactive lymphocyte (Figs. 73 and 74, Table 33). Cells typically contain multiple nucleoli and a moderate amount cytoplasm. Variable numbers of background tingible body macrophages are seen. The most common cytomorphic appearance of DLBCL is the centroblastic type (205). Rare variants of DLBCL include immunoblastic, plasmablastic, and

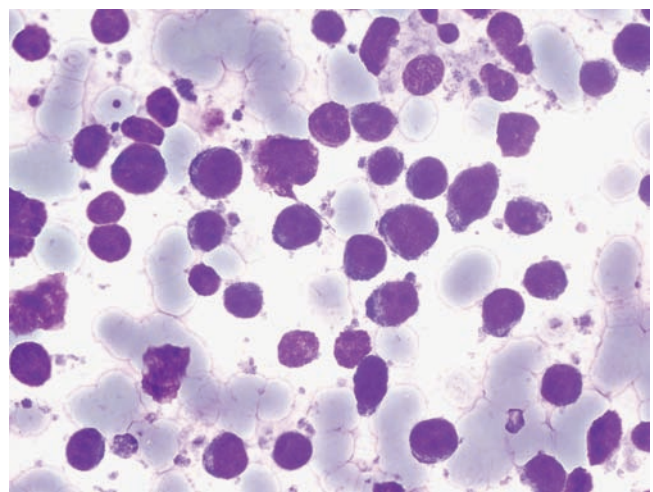


Figure 73 An aspirate from a diffuse large B-cell lymphoma with proliferation of numerous large, noncleaved lymphocytes with a few smaller mature lymphocytes in the background (DQ stain; oil magnification, 600 $\times$).

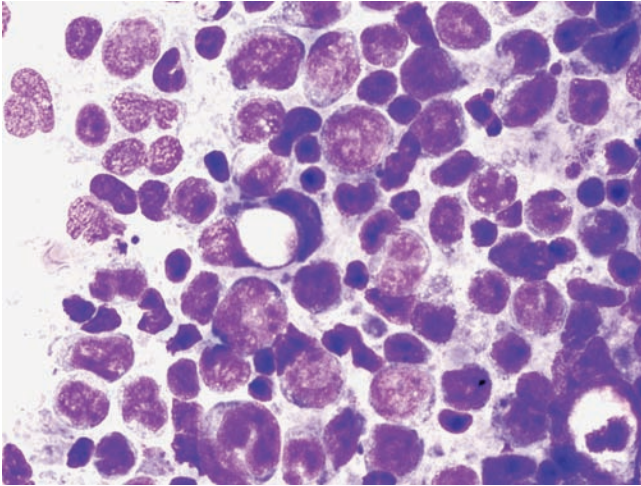


Figure 74 The nuclei from diffuse large cleaved B-cell lymphomas show nuclear clefting and indentations and smaller mature lymphocytes are present in the background (DQ stain; oil magnification, 600×).

Table 33 Key Diagnostic Features—Diffuse Large B-Cell Lymphoma

Monomorphic large cells with a minority of small lymphocytes
Cells 3 or more times the size of mature lymphocytes
Large pleomorphic nuclei; round to irregular to multilobated and bizarre shaped
Conspicuous nucleoli; single or multiple
Moderate to abundant cytoplasm
Necrosis and tangible body macrophages common
Morphologic variants: centroblastic, anaplastic, immunoblastic, T-cell rich

anaplastic types (205). In cases with a mixture of small and large cells, caution should be taken, and ancillary tests such as flow cytometry and IHC should be carefully evaluated to rule out any small cell lymphomas. Nearly all DLBCL expresses pan B-cell markers such as CD19, CD20, CD22, CD79a, and Pax5. Demonstration of a large cell predominant lymphoma with expression of one or more of these markers is sufficient for a diagnosis. Other than pan B-cell antigens, DLBCL usually lacks specific antigen expression (238). An MCL can be ruled out by a predominance of large cells with centroblast morphology and lack of cyclin D1 expression or rearrangement. A definitive diagnosis of DLBCL by FNA usually requires the demonstration of clonality, which can be achieved by flow cytometry or PCR. Since flow cytometry has become a routine procedure in lymph node FNA in many institutions, establishment of clonality should be first attempted by this method. Detection of a clonal B-cell population by flow cytometry also rules out HL. A concurrent core needle biopsy (CNB) is a useful adjunct to FNA in the diagnosis of DLBCL because sufficient material to render a definitive diagnosis can usually be obtained when FNAB is nondiagnostic (212). Observation of a

diffuse pattern is essential since a nodular process may indicate a high-grade follicular lymphoma. A B-cell phenotype is generally established by CD20 immunohistochemical studies but patients who previously received rituximab (anti-CD20 antibody) treatment may completely lose CD20 expression in the lymphoma cells. However, other B-cell markers such CD79a or Pax5 can be used for immunophenotyping.

Immunoblastic Lymphomas

Immunoblastic lymphomas are more often seen in adults than in children. The aspirates yield highly cellular smears containing numerous immunoblasts with extreme pleomorphism and scattered multinucleated giant cells. Nuclei often exhibit a plasmacytoid appearance with eccentric vesicular nuclei with a prominent central macronucleolus, and abundant cytoplasm (Fig. 74). Mitotic activity is brisk and the background contains mixed inflammatory cells including eosinophils, plasma cells, lymphocytes, and histiocytes.

Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) (Table 34) accounts for 3% of adult NHL and 10% to 30% of childhood lymphomas. Aspirates may be polymorphic due to partial involvement of lymph nodes where the neoplastic cells may be confined to the sinusoids thus leading to potential sampling errors. Generally, FNAB smears are characterized by large, pleomorphic cells, often with a horseshoe-shaped nucleus (so-called “hallmark” cells) (Fig. 75) (178,239–242). Necrosis may be prominent (241). Variants include the small cell type, the lymphohistiocytic variant, in which a large number of histiocytes may mask the large tumor cells, the rare signet cell variant, the neutrophil-rich variant, and the sarcomatoid variant. Binucleate, Reed-Sternberg-like cells may be seen, and have been mistaken for lymphocyte-depleted HL (Fig. 76) (243).

Immunophenotyping of ALCL shows that cells are usually of T-cell lineage. It is somewhat unique in that CD3, CD5, and CD7 expression are usually lost and usually the only indication of T-cell differentiation is expression of CD2 and CD4. Occasional cases are immunophenotypically null cell type, but show rearrangement of the T-cell receptor genes. ALCL also expresses CD30 in either a membranous or Golgi pattern, in addition to epithelial membrane

Table 34 Key Diagnostic Features—Anaplastic Large Cell Lymphoma

Moderate to high cellularity smears
Predominant large malignant cells with marked pleomorphism
Multinucleation common with mirror image Reed-Sternberg-like cells
“Hallmark” cells: large cells with eccentric indented nuclei, small nucleoli, prominent golgi zone and abundant cytoplasm
Intranuclear inclusions, nuclear membrane convolutions, conspicuous nucleoli
Abundant cytoplasm with fine to coarse vacuoles
Lack or absence of other lymphoid cells on smears

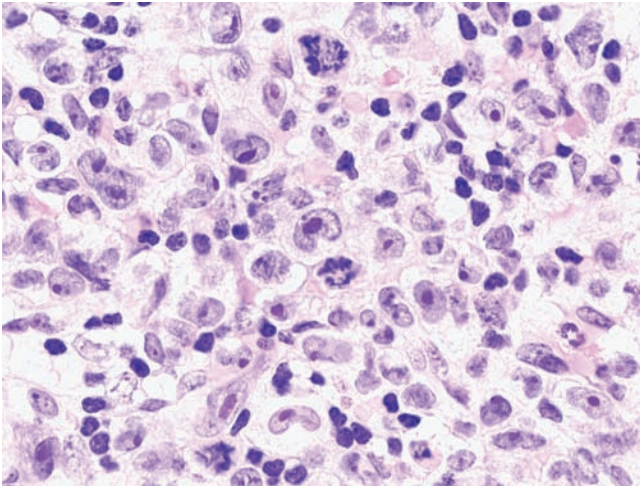


Figure 75 A core needle biopsy from anaplastic large cell lymphoma illustrating large pleomorphic cells, some with a horseshoe shape (“hallmark cells”, center of field) (H&E stain; magnification, 400×).

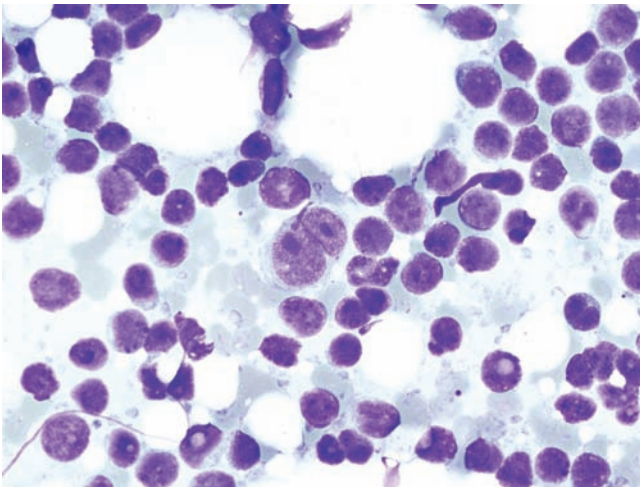


Figure 76 The presence of binucleate, Reed-Sternberg-like cells in cases of anaplastic large cell lymphoma can raise the possibility of lymphocyte-depleted Hodgkin lymphoma (DQ stain; oil magnification, 600×).

antigen (EMA) and T-cell intracellular antigen (TIA)-1. This staining pattern can lead to a confusion with metastatic carcinoma or HL. Genetically, 60% to 85% of ALCL are associated with the translocation t(2;5) (p23;q35), which results in expression of the anaplastic lymphoma kinase (ALK) protein which can be demonstrated either by flow cytometry or by IHC on cell block preparations (178,239). ALK-positive ALCL is most common in children and young adults with a marked male predilection and is associated with a better prognosis (239). By contrast, ALK-negative neoplasms are seen in older patients and with no gender predilection (239).

The presence of large neoplastic cells in a lymph node aspirate raises the differential diagnosis of ALCL, large cell lymphoma, HL, metastatic carcinoma, embryonal carcinoma, lymphoblastic lymphoma, sarcoma, and some peripheral T-cell lymphomas. Embryonal carcinoma, HL, and many metastatic carcinomas commonly express CD30. Rare examples of each of the other entities in this differential may also express CD30. A polymorphous lymphoid background is seen in both HL and ALCL and can lead to a misdiagnosis (244). Both HL and ALCL show CD30 reactivity, but the higher proportion of larger atypical cells may be helpful in identifying ALCL. In cases where the atypical cells are confined to subcapsular sinuses, the findings on FNAB and excision of the lymph node will simulate metastatic carcinoma or primary HL (240).

G. B-Cell Non-Hodgkin Lymphoma of Small Cell Type

In the WHO classification, this category includes SLL, MCL, follicular center cell lymphoma, marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL) (205). All demonstrate smears with small, mature-appearing lymphocytes and all may contain larger cells, such as immunoblasts (SLL and MZL), plasma cells (LPL), histiocytes (in MCL), centroblasts, and dendritic cells (in follicular lymphoma). The entities are distinguished by a combination of morphology, immunophenotype, and cytogenetics (Table 35) (212). In general, FNAB has a high sensitivity for diagnosis and classification of SLL, low-grade follicular lymphoma, MCL, and LPL. FNAB, however, has been less reliable for the diagnosis of MZL (207,216,217,231).

Table 35 Immunophenotyping of Small B-Cell Lymphomas (WHO Classification)

Immunophenotype	Small lymphocytic lymphoma	Mantle cell lymphoma	Follicular lymphoma	Marginal-zone lymphoma
CD5	+	+	–	–
CD10	–	–/+	+/-	–
CD23	+	–	–/+	–
Cyclin D1	–	+	–	–
CD43	+	+	–	–/+
Cytogenetics	trisomy 12	t(11;14)	t(14;18)	

Source: Modified from Ref. 212.

Small Lymphocytic Lymphoma

SLL is most often seen in older adults, with a male predominance. Patients usually have diffuse lymphadenopathy at the time of diagnosis and with involvement of both peripheral blood and bone marrow. The clinical disease course is often indolent but progressive. Aspirates are generally highly cellular and are characterized by a monomorphous population of small, mature-appearing lymphocytes with smooth nuclear borders, clumped chromatin, and scant cytoplasm (Fig. 77) (245). Mitotic figures and nucleoli are generally absent. A small component of larger cells, including prolymphocytes with a distinct nucleolus and more cytoplasm as well as paraimmunoblasts with a more prominent nucleolus and more basophilic cytoplasm, can be seen and may be confused with Reed-Sternberg cells of HL. Tingible body macrophages and lymphohistiocytic aggregates are usually absent. Because of the predominance of small, mature-appearing lymphocytes, SLL can be an important cause of a false-negative FNA. Transformation to large cell lymphoma (Richter's syndrome) can occur in 10% to 20% of cases. Features suggestive of transformation include increased numbers of prolymphocytes and paraimmunoblasts, increased mitotic figures, and the presence of apoptosis and necrosis (246). Immunophenotyping of SLL shows low-intensity CD20 and immunoglobulin light chain expression, and coexpression of CD5 and CD23, the latter combination being highly specific for SLL. Caution should be given when CD23 expression is low or heterogeneous, which can be seen in MCL. The presence of trisomy 12 or deletion of 13q14 (RB1) favors SLL. These chromosome abnormalities can be demonstrated by FISH on FNAB smears (216,247).

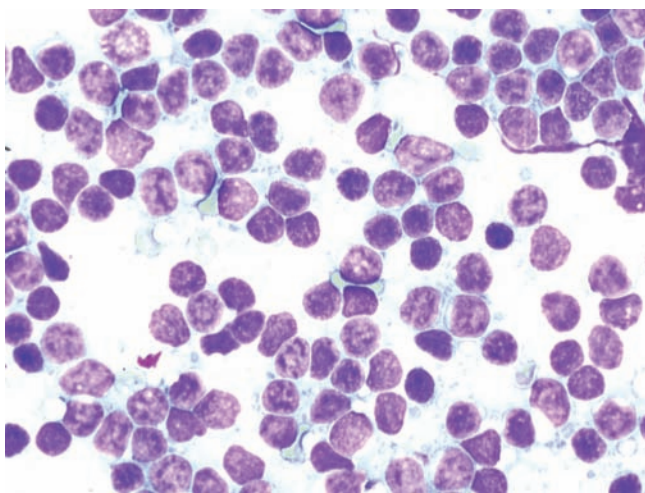


Figure 77 Aspirates from small lymphocytic lymphomas are characterized by a monomorphous population of small, mature-appearing lymphocytes with smooth nuclear borders, clumped chromatin, and scant cytoplasm (DQ stain; oil magnification, 600 $\times$).

Mantle Cell Lymphoma

MCL is seen in adults over 50, with men affected twice more often than women, and it is more aggressive than other small cell lymphomas. Unlike other small cell lymphomas, it tends to present at a higher stage and commonly found in extranodal sites such as spleen and bone marrow. FNAB from MCL is characterized by a monomorphous small cell population with scant cytoplasm, resembling centrocytes (212,248,249). Nuclear chromatin is fine and evenly dispersed, and slightly irregular nuclear outlines than those in SLL are seen. Large transformed cells such as centroblasts and immunoblasts are usually not seen as in other small cell lymphomas. Histiocytes are commonly seen in MCL, but tingible body macrophages are rarely found. Several morphologic variants have been described in MCL. The blastoid variant is most common and is characterized by neoplastic cells that are intermediate to large in size, resemble lymphoblasts and demonstrate nuclei with slightly irregular contours, fine evenly distributed chromatin, and several small distinct nucleoli. It is important to differentiate blastic MCL from lymphoblastic lymphoma (250).

Flow cytometry is an essential component in the FNA diagnosis of MCL, which expresses a monoclonal B-cell phenotype with a high intensity of surface B-cell antigens and immunoglobulin light chain (212). MCL shows a characteristic CD5-positive/CD23-negative immunophenotype. Almost all cases of MCL are associated with a translocation involving cyclin D1 and immunoglobulin heavy chain genes, t(11;14)(q13;32), leading to upregulation of the cyclin D1 protein. The nuclear expression of cyclin D1 can be detected on cell block preparations or on air-dried smears by immunohistochemistry (178). FISH is the method of choice in detecting cyclin D1 rearrangement at the genomic level and has been successfully performed on FNAB material (251).

A definitive diagnosis of MCL by FNAB requires a combination of typical cytomorphologic findings, a monoclonal B-cell population, CD5-positive/CD23-negative phenotype, and demonstration of cyclin D1 overexpression or rearrangement (232,251). The morphologic and phenotypic overlap between MCL and SLL can be a challenge for distinguishing between these entities by FNAB findings alone.

Follicular Lymphoma

Follicular lymphoma is also generally seen in patients over 50 with a slight female predominance. As with MCL, follicular lymphoma tends to be widely disseminated at the time of diagnosis. FNAB smears are characterized by small, irregular lymphocytes with notched and convoluted nuclei (centrocytes), few associated tingible body macrophages, and lymphoid cell aggregates (212). Larger-cleaved and noncleaved lymphocytes are also seen and appear in proportion to the grade. Often there is enough material on a cell block preparation to appreciate a follicular architecture. Immunohistochemical stains are useful to demonstrate CD21-positive dendritic cells within follicles

and CD3-positive T cells at the periphery of follicles. A definitive diagnosis of follicular lymphoma requires the presence of centrocytes, centroblasts, and B-cell monoclonality. Centrocytes (also known as small-cleaved cells) are characterized by small, irregular lymphocytes with notched and folded nuclei, indistinct nucleoli, and scant cytoplasm. Centroblasts (also known as large noncleaved cells) have large round or oval nuclei with open chromatin and several small, membrane-bound nucleoli and amphophilic cytoplasm (212).

The diagnosis of follicular lymphoma requires either expression of CD10 by flow cytometry on the neoplastic cells or evidence of Bcl-2 rearrangement, a result of the translocation t(14;18)(q32;q21) that is seen in 70% to 95% of cases of follicular lymphoma and can be demonstrated at the genomic level by either FISH or PCR (252). It must be remembered that the Bcl-2 rearrangement is not unique to follicular lymphoma, as a subset of DLBCL also shows this translocation. Therefore, a combination of cytomorphology and flow cytometry more accurately separates low-grade lymphomas from DLBCL. Transformation of follicular lymphoma to LBCL occurs in 25% to 35% of patients and is associated with treatment failure and rapid progression. Since follicular lymphoma is often widespread at the time of diagnosis and transformation may only occur in some nodes and not others, FNAB has the advantage of allowing for multiple site sampling whereas obtaining multiple open biopsies would not be feasible (253).

H. FNAB of Hodgkin Lymphoma

Hodgkin Lymphoma

HL accounts for approximately 30% of all lymphomas and generally affects young adults, with a second peak in middle-aged patients. Supraclavicular, cervical, and mediastinal lymph nodes are most often affected and generally, a small number of neoplastic cells (Hodgkin and Reed-Sternberg cells) are seen in a predominant heterogeneous background of nonneoplastic cells (Table 36). There are four subtypes of classical HL: nodular sclerosis, lymphocyte-rich, mixed cellularity, and lymphocyte-depleted. The

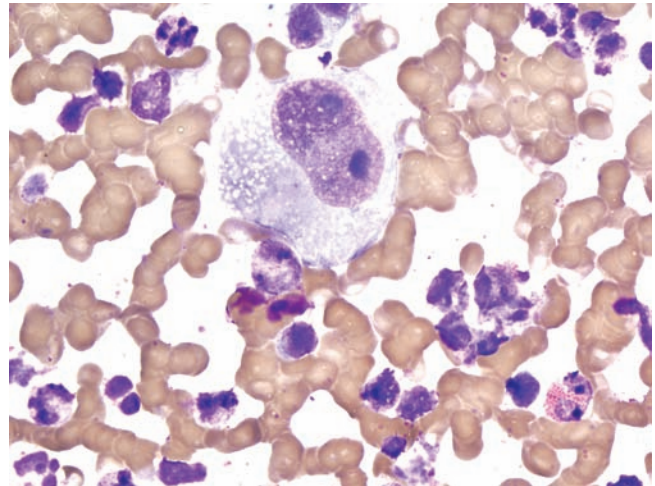


Figure 78 A binucleated Reed-Sternberg cell in a mixed inflammatory background from a case of Hodgkin lymphoma (DQ stain; oil magnification, 600×).

fifth category is nodular lymphocyte predominant HL, comprising approximately 5% of cases.

Classical HL. Classical HL accounts for 95% of cases. There is an association with prior infectious mononucleosis. The majority of patients present with mediastinal and cervical lymphadenopathy, which is typically painless. The key to an FNAB diagnosis of HL is the identification of Reed-Sternberg cells in a mixed background of non-neoplastic cells (Fig. 78). The classic Reed-Sternberg cell is binucleate, with prominent nucleoli, often the size of an RBC. These cells are very large measuring between 40 and 100 μm . However, Reed-Sternberg cells are generally the minority population in a polymorphous background composed of non-neoplastic lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells, and fibroblasts. This admixture of background cells is common to all HL subtypes and granulomas may also be seen. In general, tingible body macrophages or lymphohistiocytic aggregates are not seen, but exceptions include partial node involvement by HL and the nodular lymphocyte predominant form (212). Immunophenotypically, the Reed-Sternberg cells of classical HL are CD15-positive, CD30-positive, CD20-negative, CD45-negative, and EMA-negative. Because of the paucity of neoplastic cells, flow cytometry has not proven useful in the diagnosis of HL. Flow cytometry usually detects the background polyclonal lymphocytes because the diagnostic Reed-Sternberg cells are too few to be analyzed.

Compared with NHLs, the FNA diagnosis of HL remains highly controversial. In general, for patients without a previous history of HL, a definitive diagnosis of HL by FNAB requires identification of multinucleated, classic Reed-Sternberg cells or Reed-Sternberg cell variants in an appropriate inflammatory background, and demonstration of appropriate antigen expression by IHC on cell block preparations using

Table 36 Key Diagnostic Features—Hodgkin Lymphoma

Smear cellularity variable from highly cellular to hypocellular
Presence of enlarged mononuclear Reed-Sternberg variants in a lymphoid background
Mononuclear Reed-Sternberg variants: enlarged four times or more size of mature lymphocytes, bosselated nuclear contours, prominent enlarged nucleoli
Classic binucleate Reed-Sternberg cells represent 0.1–1% of all cells in classic Hodgkin lymphoma
Differential diagnosis of Reed-Sternberg cells:
Immunoblasts
Anaplastic large cell lymphoma
Malignant melanoma
Pleomorphic sarcoma
Large cell carcinoma

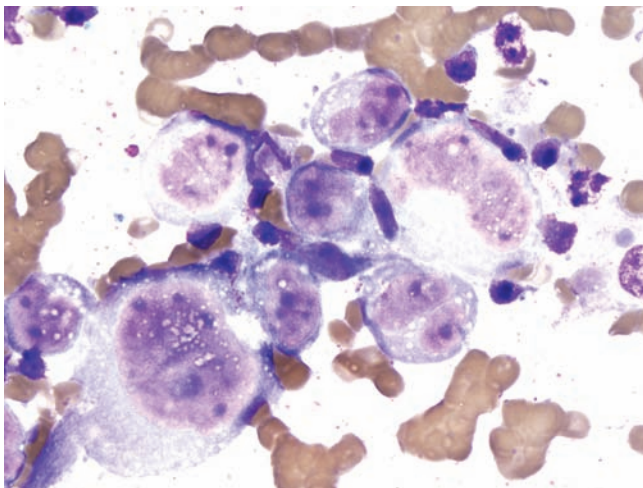


Figure 79 Mononuclear Reed-Sternberg cell variants with prominent nucleoli are commonly seen. Their presence in a mixed inflammatory cell background should strongly suggest Hodgkin lymphoma (DQ stain; oil magnification, 600 $\times$).

CD20, CD30, CD15 and CD45 (254). For patients with recurrent disease, the identification of RS cells or its variants in a proper inflammatory background is sufficient for diagnosis (Fig. 79). A concomitant CNB can be a very useful addition to FNA. An adequate CNB can provide valuable architectural information such as nodularity and fibrosis in the nodular sclerosis subtype of classical HL. A full panel of IHC can then be performed on the CNB to confirm the diagnosis.

The cytologic differential diagnosis of HL includes reactive hyperplasia, T-cell-rich large B-cell lymphoma, anaplastic large cell lymphoma, metastatic carcinoma, and metastatic melanoma (222). A false-negative FNAB diagnosis may result from the aspiration of inadequate numbers of diagnostic Reed-Sternberg cells because of partial involvement of the node or sampling of a fibrotic process such as a case of nodular sclerosis HL. In a clinically suspicious case, a careful search for Reed-Sternberg cells is necessary. The relative paucity of Reed-Sternberg cells in most forms of HL (even with adequate sampling) can still lead to the misdiagnosis of a reactive hyperplasia. Conversely, certain reactive and neoplastic conditions, such as Epstein-Barr infection, NHLs (i.e., ALCL), and certain immunosuppression states may contain large atypical cells resembling Reed-Sternberg cells leading to a false-positive diagnosis. It is therefore recommended that any FNAB smear containing granulomatous inflammation be evaluated carefully for Reed-Sternberg cells. CD15 can stain some carcinomas, and some cases of HL can express EMA leading to a misdiagnosis of metastatic disease. Among lymphoid neoplasms, the important differential diagnoses of HL include ALCL and LBCL (Table 36). Cytologically, ALCL cells are indistinguishable from Reed-Sternberg cells (Fig. 76). Phenotypically, ALCL expresses strong CD30 and may express weak CD15. In these cases,

demonstration of T-cell antigen or ALK expression virtually rules out HL. LBCL may express CD30 in as many as 70% of cases and the tumor cells typically lack surface immunoglobulin expression. In contrast to HL, LBCL is more monomorphous and lacks an inflammatory background. Strong, uniform expression of one or more B-cell antigens favors LBCL.

A small portion of nodular sclerosis HL contains confluent sheets of large cells known as the syncytial variant of HL. In such cases, FNAB smears are dominated by flat sheets of large Reed-Sternberg variant cells in a pleomorphic background leading to a misdiagnosis of metastatic carcinoma in some cases.

I. FNAB of Metastatic Neoplasms to Cervical Lymph Nodes

Most cervical lymph nodes with metastases are four times larger in size than normal lymph nodes. FNAB is the preferred method for the initial evaluation of adult patients with enlarged lymph nodes with an overall diagnostic accuracy of 96% for carcinomas and 100% for malignant melanomas (200,213). Metastatic disease is by far a more common cause of cervical lymphadenopathy than malignant lymphomas, especially in patients older than 50 years. Use of ancillary techniques (i.e., immunostains on cell block preparations) permits histologic subtyping and can determine the primary site.

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common malignancy to metastasize to head and neck lymph nodes accounting for 90% of malignancies arising at this site. Most are found in patients older than 40 years age and those with a history of alcohol and tobacco use. These lesions can be cystic in nature presenting some unique diagnostic difficulties. Aspirates from cystic squamous cell carcinomas are often of low cellularity containing anucleated cells or cells with only mild cytologic atypia, with background abundant proteinaceous or necrotic debris. The background often contains neutrophils and/or lymphocytes. Identification of neoplastic squamous cells is critical in distinguishing metastases from soft tissue abscesses or an inflamed branchial cleft cyst. The presence of necrotic debris with associated acute inflammation should suggest a malignancy.

Smears obtained for metastatic squamous cell carcinomas show high cellularity arranged in cohesive flat sheets, nests of cells and/or single cells occasionally with spindle to irregular shaped cells (Figs. 80 and 81). Variable keratinization can be identified best on Papanicolaou-stained smears. Individual keratinized malignant cells can be found in most smears with bizarre shapes such as tadpole and spindle shapes. The degree of cellular atypia varies with well-differentiated carcinomas demonstrating only slight nuclear enlargement and atypia, whereas poorly differentiated carcinomas demonstrated marked pleomorphism, nuclear enlargement, and nuclear irregularities. Distinct nuclear membranes, moderate to

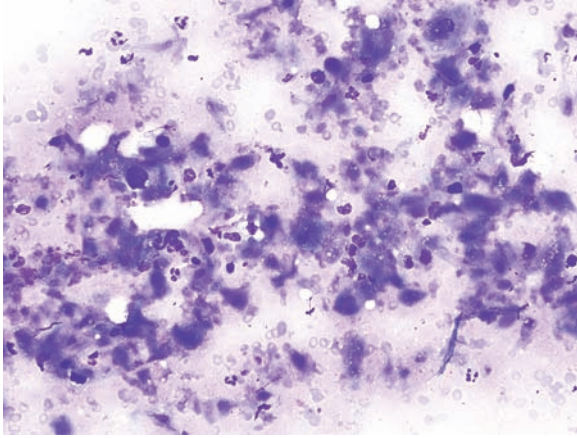


Figure 80 Aspirate from a metastatic keratinizing squamous cell carcinoma. The cytoplasm is deep blue in DQ-stained sections. Note the “dirty” background which is often seen with metastases from squamous cell carcinomas (DQ stain; magnification, 400 $\times$).

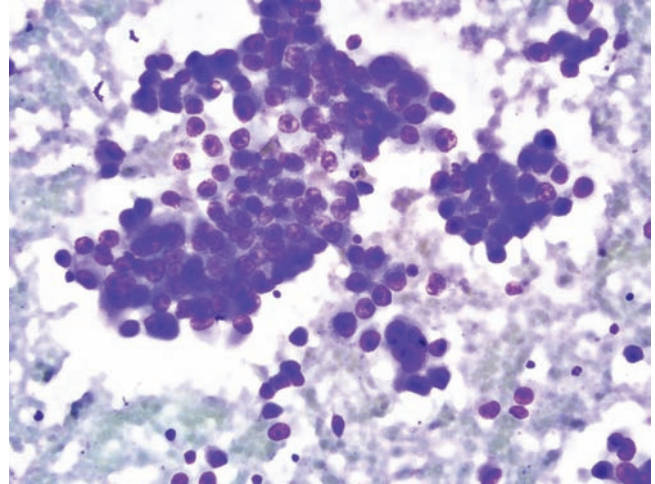


Figure 82 Aspirate from a case of metastatic nasopharyngeal carcinoma with cohesive clusters of malignant epithelial cells and a few scattered lymphocytes in the background (DQ stain; magnification, 400 $\times$).

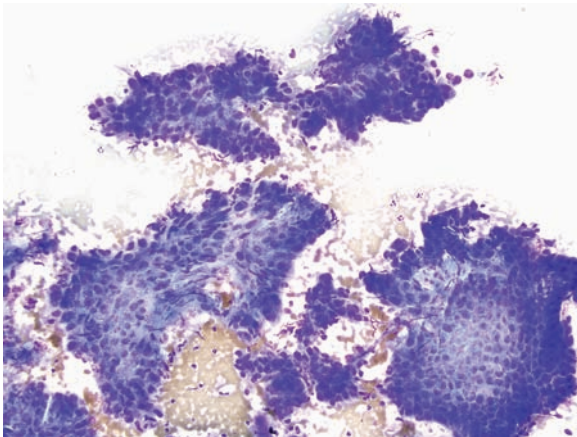


Figure 81 Large cohesive clusters of malignant cells, some with a spindled pattern, from a lymph node aspirate containing metastatic squamous cell carcinoma (DQ stain; magnification, 400 $\times$).

abundant cytoplasm and retention of some cohesive clusters are seen even in nonkeratinizing squamous cell carcinomas.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma exhibits a bimodal age distribution with peaks during the second and sixth decades of life, with males being affected 2.5 times more often than females, and is associated with EBV infection (255). Asians are more often affected than Caucasians. Patients often present with nasal symptoms in combination with cervical lymphadenopathy. FNAB smears demonstrate high cellularity with clusters and sheets of

cells within a background of reactive lymphoid cells (Fig. 82). Individual malignant cells with marked nuclear pleomorphism can also be seen dispersed among the non-neoplastic lymphoid cells (255). A small percentage can show squamous cell differentiation with a basaloid appearance. Differential diagnostic considerations include malignant lymphoma and in young patients, embryonal carcinoma. Positive immunostains for cytokeratin and negative stains for CD45 can confirm the epithelial nature of a nasopharyngeal carcinoma. Most cases of embryonal carcinoma will show positive staining with α fetoprotein, and CD30 and scattered β -human chorionic gonadotrophin (β -HCG) positive syncytiotrophoblasts.

Thyroid Carcinoma

Thyroid carcinoma metastases are a significant cause of cervical lymphadenopathy, and papillary carcinoma of the thyroid can initially present with cervical adenopathy in more than 10% of patients (256). Cytologically, the smears demonstrate small clusters of neoplastic cells with characteristic cytomorphologic features of papillary carcinoma (nuclear grooves and intranuclear inclusions best identified on Papanicolaou-stained smears) (Fig. 83) (256). Occasionally, colloid may be seen in the background. Medullary carcinoma can also be a source of metastases to cervical lymph nodes.

Malignant Melanoma

Malignant melanoma often metastasizes to cervical and supraclavicular lymph nodes even when the primary site is unknown. FNAB smears are highly cellular with loosely cohesive and singly dispersed cells with a wide range of cytologic features including spindle cell, epithelioid, plasmacytoid, small cell like, and giant cell morphologies (Figs. 84–86). Metastatic melanoma often

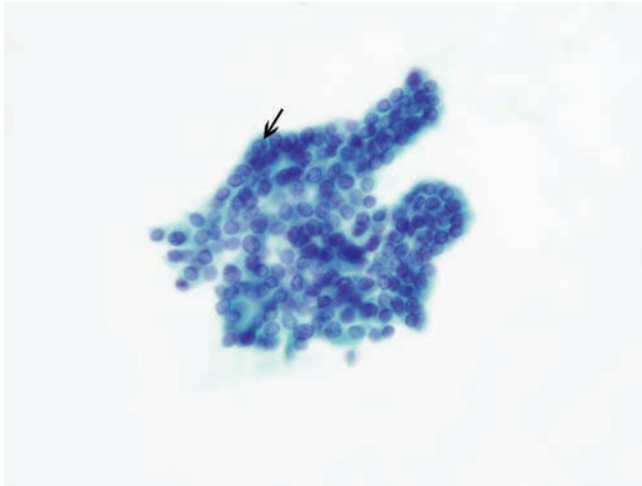


Figure 83 Fine needle aspirate from a metastatic papillary carcinoma demonstrating a papillary cluster of malignant cells with slight nuclear enlargement and nuclear grooving (*arrow*) (Papanicolaou stain; magnification, 400 $\times$).

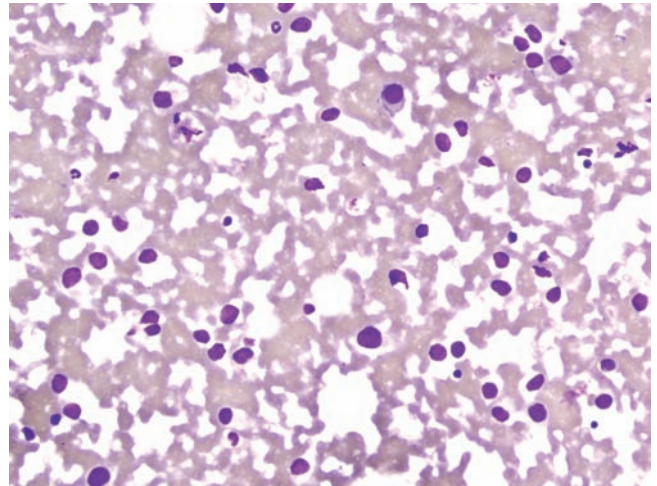


Figure 85 Lymph node aspirate from metastatic malignant melanoma with a discohesive population of large malignant cells mimicking a lymphoma (DQ stain; magnification, 400 $\times$).

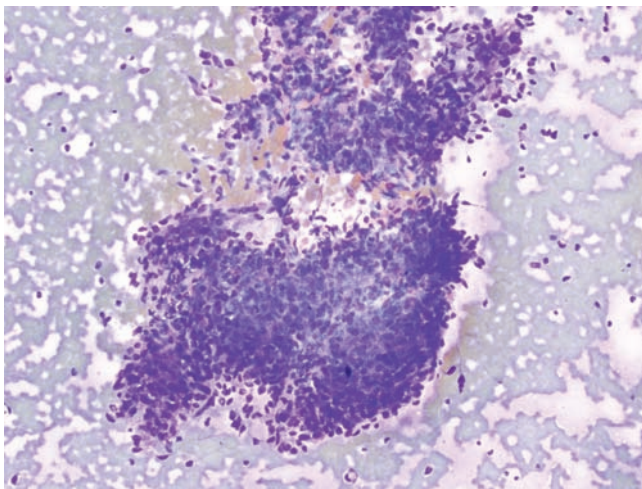


Figure 84 Aspirate from metastatic malignant melanoma with large cohesive sheets and clusters of spindle-shaped cells (DQ stain; magnification, 200 $\times$).

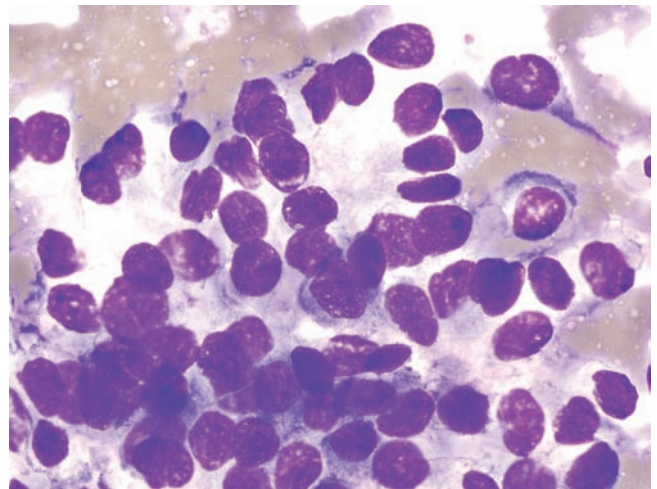


Figure 86 Loosely cohesive clusters of malignant plump plasmacytoid cells from an aspirate of metastatic malignant melanoma (DQ stain; magnification, 600 $\times$).

shows a singly dispersed cell pattern similar to NHLs (Fig. 85). Macronucleoli and nuclear pseudoinclusions are often seen. Melanin pigment is only seen in a minority of cases. In cases where a primary melanoma diagnosis has not been established, confirmation with immunostains (HMB-45, MART-1, S-100) on cell block material will be necessary.

Supraclavicular Lymph Node Metastases

Left supraclavicular lymph node metastases often originate from malignancies arising below the (often referred to as Virchow's node) clavicle or the dia-

phragm. Primary sites of origin are from malignancies above and below the diaphragm including the lung, breast, stomach, prostate, ovary, colon, biliary tract, pancreas, and uterus. FNAB is valuable for documenting metastases from inoperable lung carcinomas to this site. In women with cervical carcinoma, supraclavicular lymph node metastases most often show squamous cell carcinoma and may be the only site of extension outside the pelvis and abdomen, portending a poor prognosis. Metastatic breast carcinoma must be considered when evaluating aspirates from women, as lymph node status is a critical predictor of clinical outcome. Immunocytochemical staining for estrogen

and progesterone receptors in FNA samples from metastatic breast carcinoma have been successfully performed on formalin-fixed cell block preparations and on Papanicolaou-stained slides. In men, disseminated disease from prostate carcinoma may first present with supraclavicular lymphadenopathy. The appearance is most often that of an adenocarcinoma. Virchow's node is often also the site of gastrointestinal metastases. Demonstration of intracytoplasmic mucin by immunostaining on cell block material can exclude adenocarcinomas of liver, renal, adrenal, and thyroid origin as well as lymphoma, sarcoma (except chordoma), and melanoma. The use of cytokeratins 7 and 20 and staining for tumor specific antigens and transcription factors can aid in determining the origin of a metastatic adenocarcinoma.

J. FNAB of Selected Nonneoplastic Lymphadenopathies

Reactive Lymphoid Hyperplasia

Reactive lymphoid hyperplasia is commonly found in aspirates from enlarged cervical lymph nodes and the most important differential diagnostic entity with malignant lymphoma. FNAB smears of reactive hyperplasia demonstrate high cellularity with a heterogeneous population of lymphoid cells, including small mature-appearing lymphocytes, larger immunoblasts, dendritic cells, follicular center cell fragments (lymphohistiocytic aggregates), and tingible body macrophages (Table 37) (Fig. 87) (219,257). Small mature appearing lymphocytes are the dominant cell population. The presence of a polymorphic lymphoid population including the presence of follicular center cell fragments and tingible body macrophages are important diagnostic clues to the reactive nature of the proliferation. However, this heterogeneous population of cells can also be misleading and found in highly proliferative malignant lymphomas raising a wide differential diagnosis that includes HL, SLL, follicular lymphoma, T-cell rich B-cell lymphoma, T-cell lymphoma, and partial involvement of a lymph node by metastatic neoplasms. Ancillary studies, including immunohistochemical stains and flow cytometry, are crucial for ruling out a malignant lymphoma (178,229). Material obtained for flow cytometry offers the advantage of evaluating a large population of cells, thereby allowing the detection of small subpopulations of monoclonal cells and/or low intensity expression of some markers that may be missed by immunohistochemistry. A reactive process is characterized by a polyclonal lymphocyte population and an admixture of B and T cells. It is important to

Table 37 Key Diagnostic Features—Reactive Lymphoid Hyperplasias

Moderate to highly cellular smears
Polymorphic lymphoid population
Single cell dispersed pattern dominant
Follicular center cell fragments common
Tingible body macrophages common
Lymphoglandular bodies in background

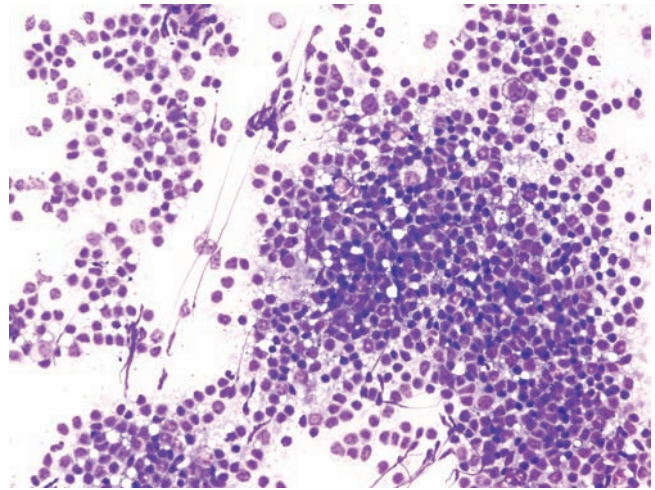


Figure 87 A mixed lymphoid cell population characteristic of reactive lymphoid hyperplasia is seen in this aspirate (DQ stain; magnification, 200 $\times$).

recognize that the lack of a monoclonal population does not rule out malignant lymphoma, especially HL. Thus, when presented with a heterogeneous lymphoid population on FNAB smears, it is crucial to search carefully for Reed-Sternberg cells and in clinically suspicious cases, additional sampling or tissue biopsy should be performed for a definitive diagnosis (217).

When small, mature-appearing lymphocytes predominate in aspirates from reactive hyperplasia, confusion with an SLL can occur (Fig. 88). However, SLLs do not show the full spectrum of small to large lymphocytes that is characteristic of a reactive process.

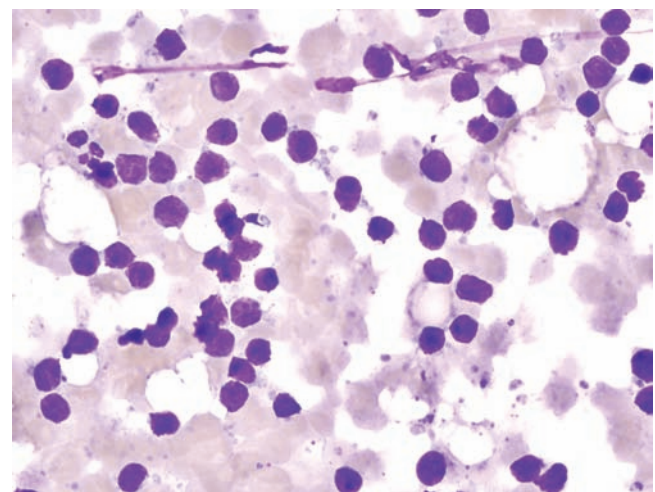


Figure 88 Some cases of reactive lymphoid hyperplasia are dominated by small lymphocytes raising the differential diagnosis of a small lymphocytic lymphoma. Note the numerous background lymphoglandular bodies indicative of a lymphoid process.

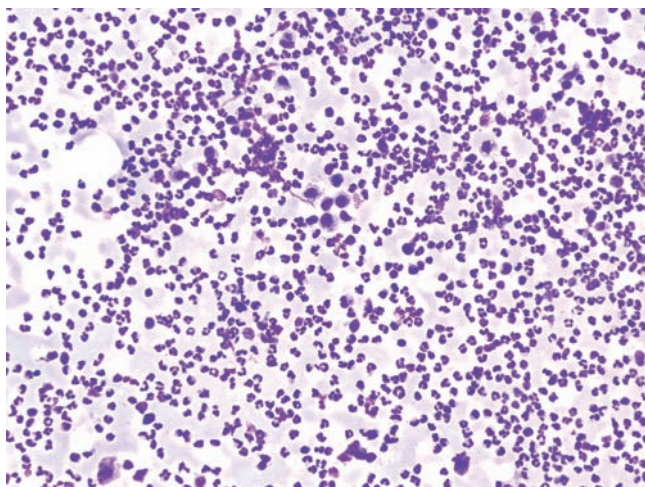


Figure 89 Aspirate from a case of suppurative lymphadenitis containing numerous polymorphonuclear leukocytes in a background containing a mixed lymphoid population.

Cellular crush artifact can cause difficulty in distinguishing small lymphocytes from a small cell carcinoma, or from lymphoblasts.

Suppurative Lymphadenitis

Suppurative lymphadenitis is most commonly seen in children and is most often caused by a bacterial infection from *Staphylococcus aureus*. Patients often present with tender, enlarged nodes with overlying erythema in the head and neck region, which may be associated with fevers. FNAB smears are generally highly cellular and characterized by many neutrophils admixed with smaller numbers of histiocytes and lymphocytes (Fig. 89). The differential diagnosis for a neutrophil-predominant FNA biopsy includes other infectious processes such as mycobacteria in AIDS and other suppurative infections such as cat-scratch disease. Neoplasms that may mimic an acute suppurative lymphadenitis include necrotic metastases (especially squamous cell carcinoma) and rare presentations of HL and anaplastic large cell lymphoma (206,258,259). Additional aspirated material should be obtained for cultures. Flow cytometric studies are not generally indicated for a neutrophil predominant FNAB smear.

Granulomatous Lymphadenitis

Granulomatous lymphadenitis can be seen in sarcoidosis, foreign body reactions, and some infections such as mycobacterial and fungal infections. Sarcoidosis is a diagnosis of exclusion, but the findings of non-caseating granulomatous inflammation in the appropriate clinical and radiographic setting may be sufficient for establishing a diagnosis (Fig. 90). The typical FNAB smear from a patient with tuberculosis reveals varying proportions of necrosis, epithelioid histiocytes, and epithelioid granulomas. The epithelioid

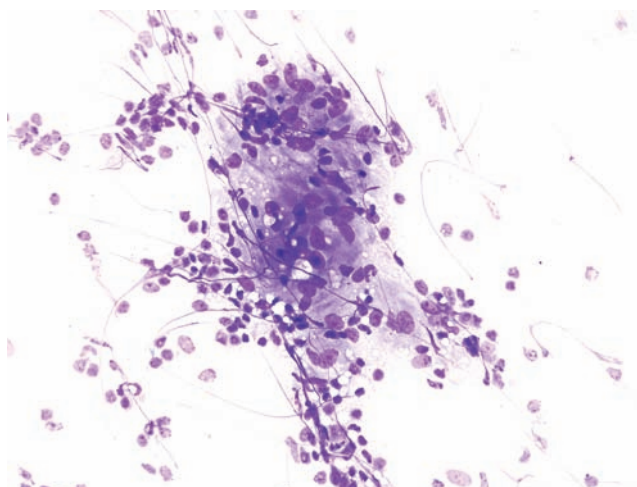


Figure 90 Well formed noncaseating granuloma from a case of sarcoidosis that is composed of cohesive “boomerang”-shaped histiocytes (DQ stain; magnification, 400×).

histiocytes possess moderate cytoplasm and a single elongated, bent (“boomerang”)-shaped nucleus with finely granular chromatin and an inconspicuous nucleolus. A background of fluffy, granular debris is often seen, along with multinucleated giant cells in varying numbers. The presence of granulomatous inflammation alone has a poor sensitivity for tuberculosis (25%) (260). In a significant number of cases, the only finding is either acute inflammation or necrosis, especially in cases of atypical mycobacterial infections in the AIDS population. On Romanowsky-type-stained FNAB smears, mycobacterial organisms may appear as “negative” images, both extracellularly and within histiocyte cytoplasm (Fig. 91) (261). Ancillary studies, including cell block preparation for special stains, cultures, and special studies such as PCR, are crucial for establishing a diagnosis. On Papanicolaou-stained smears, the organisms may exhibit autofluorescence, providing a quick, inexpensive means for identification. Occasional examples of HL may mimic a granulomatous lymphadenitis.

Toxoplasmosis

Toxoplasmosis is often asymptomatic and is caused by infection with the protozoan, *Toxoplasma gondii*. In immune-competent patients, the most common presentation is of posterior cervical lymphadenopathy. FNA smears show characteristic clusters of small histiocytic cells with abundant cytoplasm and eccentric oval nuclei, forming “microgranulomas” (262–265). The background is composed of a mixed lymphoid population, reactive follicular center cell fragments, and tingible body macrophages reflecting the histologic findings of small epithelioid clusters opposed to germinal centers. The causative organisms, both bradyzoites and tachyzoites, can be seen in a minority of FNAB smear preparations (262,266). The combination of these

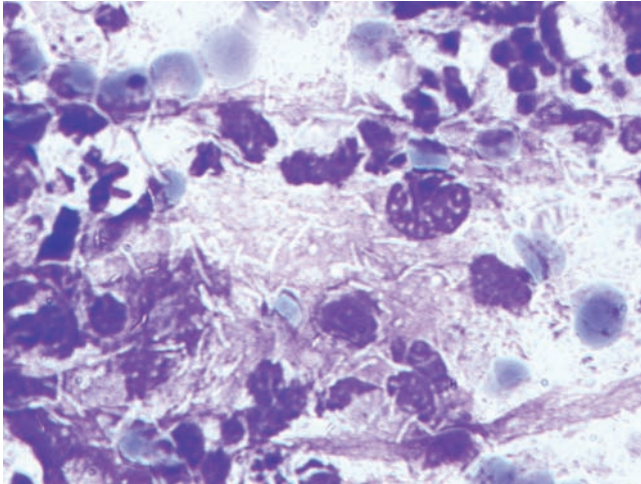


Figure 91 Characteristic and diagnostic “negative images” can be seen in DQ-stained smears in cases of mycobacterial infections, especially from immunocompromised patients with infections from *mycobacterium avium intracellulare* (DQ stain; oil magnification, 1000×).

cytologic findings along with the subsequent confirmation by serology can avoid a surgical procedure for this self-limited process (267). An ELISA method for IgM and IgG antibodies against *T. gondii* detects up to 90% of cases (268). The differential diagnosis for toxoplasmosis includes other causes of a granulomatous lymphadenitis. There are no multinucleate giant cells, necrosis, or acute inflammation as seen in cases of tuberculosis and fungal infections (267).

Cat-Scratch Disease

Cat-scratch disease is one of the more common causes of lymphadenopathy in both children and adults; and 90% of patients have had contact with cats, and the lymphadenopathy occurs one to three weeks after the initial scratch. Cervical lymph nodes can be involved, often unilaterally (posterior triangle nodes), and there is often an associated rash and fever. FNAB smears generally shows the appearance of a reactive lymph node with a mixed population of lymphocytes, neutrophils, tingible body macrophages, and follicular center cell fragments (Table 38) (269). Although seen in a minority of cases, the most distinctive finding in cat-scratch disease is the presence of microabscesses and suppurative granulomas composed of aggregates of epithelioid histiocytes arranged in a peripheral palisade with central neutrophils. The causative organism, *Bartonella henselae*, may occasionally be demonstrated by Warthin-

Starry and modified Steiner stains but, in our experience, is usually negative (270). Therefore, serologic studies may be helpful. The cytomorphologic findings in cat-scratch disease present in three stages, each of which may be confused with other processes. The early phase is characterized by a dense reactive lymphoid smear pattern with only few granulomas and no supuration or necrosis. This stage raises a differential diagnosis of reactive hyperplasia, infectious mononucleosis, follicular lymphoma, and HL. The suppurative phase (second or third week) is characterized by a marked neutrophilic infiltrate and stellate granulomas along with a minor component of necrosis. Differential diagnostic considerations include a suppurative lymphadenitis and lymph node infarction (267,271). By the third or fourth week, a necrotizing stage is seen characterized by extensive necrosis and fibrin deposition that may obscure the granulomas present. The differential diagnosis at this stage includes Kikuchi lymphadenitis, granulomatous lymphadenitis, lymphoma, and metastatic carcinoma.

Infectious Mononucleosis

Infectious mononucleosis is the most common of the benign lymphoproliferative disorders, is caused by the EBV, and is most often seen in adolescents. Patients present with fever, pharyngitis, splenomegaly, and atypical lymphocytosis in the peripheral blood. Lymphadenopathy is most often seen in the cervical region. In the era of serologic testing and the monospot test, a biopsy is rarely necessary. However, FNAB has been useful in cases with a protracted clinical course or an unusual presentation where malignant lymphoma enters into the differential diagnosis. FNAB smears are highly cellular and resemble reactive lymphoid hyperplasia, with a mixed population of small and large lymphocytes, lymphohistiocytic aggregates (follicular center cell fragments), lymphoblasts, and plasmacytoid lymphocytes (272,273). In some cases, immunoblasts are numerous and appear as large mononuclear cells with a smooth nuclear outline, evenly dispersed chromatin, a large central nucleolus, and abundant basophilic cytoplasm (Fig. 92). Binucleated immunoblasts can be confused with Reed-Sternberg cells of Hodgkin's disease. Immunostains for CD15 and CD30 are helpful as they are negative in immunoblasts. The large number of immunoblasts should raise the possibility of mononucleosis or other viral infections but it also creates confusion with a neoplastic process (267). However, the pleomorphism of the immunoblasts should lead one to suggest mononucleosis rather than a lymphoma. Immunostains show a mixture of B cells and T cells with a CD8 phenotype (274). The differential diagnosis also includes reactive hyperplasias, follicular lymphoma, and large cell lymphoma. An abundance of large immunoblasts may also lead to confusion with metastatic carcinomas or malignant melanoma (267).

Rosai-Dorfman Disease

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a rare idiopathic proliferative disorder that typically affects male children or

Table 38 Key Diagnostic Features—Cat-Scratch Disease

Moderate to highly cellular smears
Neutrophils with variable background necrosis, karyorrhectic debris
Granulomas (few to many)

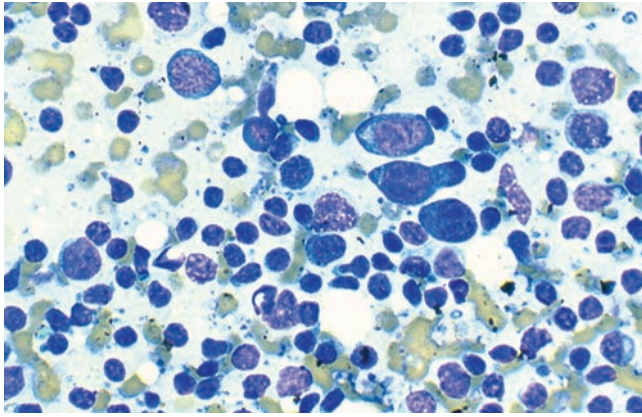


Figure 92 Aspirate from a case of infectious mononucleosis containing numerous immunoblasts with increased pleomorphism in a mixed lymphoid background (DQ stain; oil magnification, 600 $\times$).

adolescents and most often leads to bilateral persistent and painless cervical lymphadenopathy. FNAB smears are highly cellular with a pattern of reactive lymphoid hyperplasia and a large number of histiocytes containing phagocytosed lymphocytes and RBCs termed “emperipolesis” (Fig. 93) (275–278). In the proper clinical setting, the cytologic findings may be conclusive. A cell block preparation can allow for immunohistochemical stains that show reactivity in the large histiocytoid cells for S-100 and CD68, but not CD1a (279). The differential diagnosis includes reactive hyperplasia, HL, and rare cases of nodal Langerhans cell histiocytosis. The histiocytes of Rosai-Dorfman disease do not exhibit the nuclear grooves

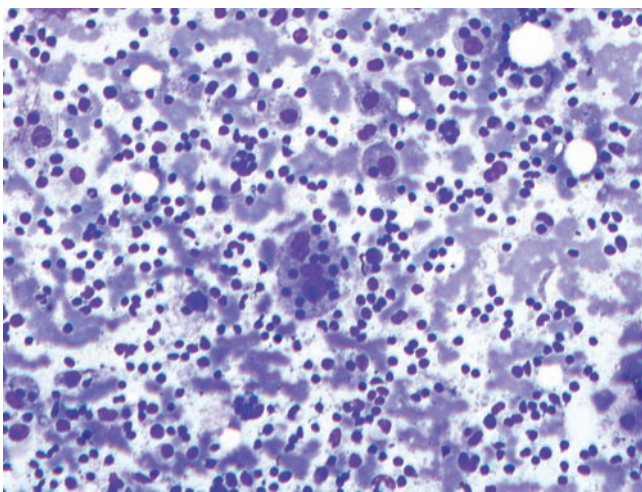


Figure 93 Aspirate from a case of Rosai-Dorfman disease showing a histiocyte containing phagocytized lymphocytes and RBCs in a background of reactive lymphoid hyperplasia (DQ stain; oil magnification, 600 $\times$).

or complex, indented nuclei of Langerhans’ histiocytes. In addition, the histiocytes of Langerhans’ cell histiocytosis co-express S-100 and CD1a (279).

Kikuchi Lymphadenitis

Kikuchi lymphadenitis is a relatively rare, self-limited disease seen in young adult women of Asian descent. The cervical lymph nodes are most often involved. FNAB smears show phagocytic histiocytes with a crescent shaped nucleus with an irregular nuclear outline, twisted contours, and inconspicuous nucleoli. The cytoplasm contains phagocytosed debris. Also seen are plasmacytoid monocytes that have eccentrically placed round nuclei with basophilic cytoplasm. Immunoblasts are seen and may be numerous. The background contains karyorrhectic and granular debris admixed with histiocytes and immunoblasts. There is an almost complete absence of neutrophils. There is significant overlap in the FNAB features of Kikuchi lymphadenitis, reactive hyperplasias, and tuberculosis (280,281). Additional differential diagnostic considerations include lymph node infarction, metastatic carcinoma (particularly squamous cell carcinoma), and high-grade lymphomas. The plasmacytoid cells may also be confused with a plasmacytoid lymphoma. The atypical cells with crescent nuclei may be confused with signet ring carcinoma (280,281).

V. SARCOMAS

A. General Considerations

As a group, soft tissue sarcomas represent less than 1% of all malignant neoplasms diagnosed in the US each year (282). Furthermore, as an overall percentage of neoplasms, the incidence is higher in children than in adults. Because of their absolute rarity and the inexperience of many practicing pathologists in dealing with the morphologic diversity of soft tissue sarcomas, most institutions have traditionally obtained diagnostic tissue from either open biopsies or closed CNBs (211,283). Therefore, most pathologists are uncomfortable making a definitive diagnosis of a sarcoma, knowing that a misdiagnosis can potentially lead to debilitating treatment such as an amputation (282,284). FNAB has been further underutilized because of the requirement of accurate histologic subtyping for enrollment of pediatric patients into histogenetic-specific therapeutic protocols (211,284). However, a number of studies have systematically evaluated the accuracy of FNAB and shown that on adequate specimens and with the judicious use of ancillary studies, there is an overall accuracy rate comparable to CNB that approaches 95% for establishing a benign versus malignant diagnosis and reported false-positive and false-negative rates of less than 1% to 4% (204,285–287). Studies evaluating the rate of accurate subtyping of soft tissue sarcomas by FNAB have shown variable results with an average of 50% to 70% (285–288). One of the largest series reported by Kilpatrick and colleagues found the accuracy rate for sarcoma subtyping of 92% in pediatric sarcomas (with

use of ancillary studies), a rate higher than that achieved in adult sarcomas (52%) (289). For pediatric small round cell tumors, histological subtyping is critical as most of these patients are eligible for enrollment in histogenetic-specific treatment protocols. In a series of 18 pediatric patients eligible for such treatment protocols, Kilpatrick and colleagues showed an accurate diagnosis by FNAB in 17 of 18 patients (94%) (285). Similar results have also been shown by Jones and colleagues supporting the opinion that FNAB can accurately subtype and grade soft tissue sarcomas in most cases (290). Grading of soft tissue sarcomas is important in both management and prognosis, but requires accurate evaluation of the percentage of tissue necrosis and mitotic rates, parameters that cannot be adequately assessed by FNAB alone. Thus, for FNAB specimens, most studies recommend a classification system dividing soft tissue sarcomas into five major subgroups on the basis of the predominant cytomorphologic phenotype seen on the aspiration smears (291). These are the small round cell, spindle cell, epithelioid/polygonal cell, myxoid, and pleomorphic sarcoma subgroups. Once a cytomorphologic phenotype has been determined, the corresponding histological grade, in most cases, becomes definitional and a two tiered grading system works best (low grade and high grade; i.e., round cell, pleomorphic, and epithelioid/polygonal subgroups are, by definition, high-grade sarcomas) (291,292). For most soft tissue sarcomas, the stage (incorporating grade) and anatomic location are used to determine therapy and in adults with high-grade sarcomas (i.e., pleomorphic and epithelioid/polygonal subgroups), the therapy is similar. As with any classification system, there are certain limitations related to the morphologic spectrum that can be seen with various soft tissue sarcomas. For example, rhabdomyosarcomas can display a variety of cytomorphologic features ranging from small round cell to spindle cell morphology. Likewise, synovial sarcoma may demonstrate a predominant epithelioid/polygonal pattern rather than the classic spindle cell pattern (211). Especially in adults, it is important to remember and rule out metastatic carcinoma, malignant lymphoma, and malignant melanoma as these lesions vastly outnumber primary soft tissue sarcomas in this age group (284).

Diagnostic Approach Including Ancillary Studies

FNAB requires a multidisciplinary approach for diagnostic success. Clinical and radiographic correlation is crucial as radiographic studies can provide information relating to location (superficial vs. deep), presence/absence of osseous involvement, size, relationship to other structures (nerves, vessels) and degree of heterogeneity (fat content, cyst formation). Correlation of these features with the cytomorphologic findings can help narrow down the differential diagnosis (284). Certain soft tissue sarcomas have a predilection for metastasizing to lymph nodes (Table 39). Patient age is a critical factor to consider, as there is little overlap in the lesions that predominate in each general age group (282,291). For example, small round cell tumors

Table 39 Sarcomas That Metastasize to Lymph Nodes

Rhabdomyosarcoma
Synovial sarcoma
Ewing sarcoma
Kaposi sarcoma
Angiosarcoma
Epithelioid sarcoma

predominate in the pediatric age group whereas myxoid and pleomorphic cell sarcomas are common in older adults (>50 years) and are virtually nonexistent in children. The epithelioid/polygonal and spindle cell groups are generally seen in young to middle-aged adults.

An interpretative approach used by most cytopathologists involves morphologic pattern recognition and categorization by the dominant cytomorphologic phenotype identified. Once a lesion has been categorized as malignant, subtyping should be attempted especially for the small round cell category (211). Ancillary studies can be extremely useful in establishing a specific diagnosis when the clinical and morphologic findings are equivocal. IHC, molecular, and genetic analysis of FNAB material play a critical role in rendering histogenetic-specific diagnoses of pediatric soft tissue sarcomas, including the small round cell sarcomas, a requirement for enrollment of patients on specific treatment protocols (i.e., Pediatric Oncology Group) (Table 40) (284,285,292,293). A panel of immunohistochemical stains plays an important role in the workup of small round cell, spindle cell, and the epithelioid/polygonal cell sarcomas. IHC screening panels are also important to separate primary soft tissue sarcomas from metastatic carcinoma, malignant melanoma, and malignant lymphoma. Although helpful, some cytogenetic and molecular studies initially thought to be highly specific for certain soft tissue sarcomas have now been shown to actually be more nonspecific. The best example is the Ewing's sarcoma translocation, t(11;22)(q24;q12) with the WES-FLI1 fusion product, which has also been reported in embryonal and alveolar rhabdomyosarcomas, neuroblastoma, and mesenchymal

Table 40 Immunohistochemical Screening Panels for Small Round Sarcomas

Rhabdomyosarcoma	MyoD1/myogenin+ Desmin+ Cytokeratin± S-100±
Ewing sarcoma/PNET	Desmin– CD56– CD99+ FLI-1+ Cytokeratin ± S-100–
Synovial sarcoma	Cytokeratin+ CD99+ EMA+ Desmin– CD34– S-100+ (30%)

Abbreviations: EMA, epithelial membrane antigen.

chondrosarcoma (285). The cytomorphology and histopathology findings (285) should always “trump” the ancillary studies. Therefore, we believe that ancillary studies should be used to supplement, not replace, the cytomorphologic findings and data obtained from such tests should be interpreted only within the context of the full clinical and cytologic findings.

B. FNAB of Benign Soft Tissue Lesions

Proliferative Myositis and Nodular Fasciitis

These pseudosarcomatous lesions can occasionally affect the head and neck region. Proliferative myositis frequently arises in the sternomastoid muscle in patients aged between 45 and 65 years. Rapid growth leads to confusion with a sarcoma. Proliferative myositis can be considered the intramuscular homolog of nodular fasciitis (284). Aspiration smears contain a mixture of skeletal muscle, reactive fibroblasts, and multinucleated cells (Table 41–42). Scattered large polygonal cells with prominent nucleoli and abundant cytoplasm may be seen. The differential diagnosis mainly includes sarcomas including rhabdomyosarcoma and malignant fibrous histiocytoma (MFH). Nodular fasciitis also represents a pseudosarcomatous response to injury that manifests as a rapidly enlarging mass (294). Peak incidence occurs in the third and fourth decades with approximately 13% occurring in the head and neck region (294). Smears are generally cellular with an admixture of single and small clusters of spindle shaped cells along with variable numbers of myxoid stromal fragments. Cells demonstrate vesicular nuclei with small multiple nucleoli and wispy cytoplasm. Mitoses are frequently seen and admixed inflammatory cells are seen admixed with stromal fragments. The cytologic smears display a “tissue-culture” appearance on low power examination. Distinction from true sarcomas of soft tissue is based on a clinical history of rapid enlargement and presence of a mobile superficial nodule.

Table 41 Key Diagnostic Features—Nodular Fasciitis

Cellular smears
Cell clusters and single cell pattern
Spindled cells with long cytoplasmic processes
Bland spindled nuclei with indistinct nucleoli
myxoid or fibrillar material may be present in background
Mixed inflammatory cell infiltrate with neutrophils, lymphocytes, histiocytes
Giant cells and pigment laden histiocytes often present

Table 42 Key Diagnostic Features—Proliferative Myositis

Cellular smears with single cells and tissue fragments
Two cell population: ganglion like giant cells and spindled cells resembling nodular fasciitis
Bland nuclear features, uniform chromatin, smooth nuclear membranes
Hemorrhagic background containing fat, metachromatic stroma

Table 43 Key Diagnostic Features—Rhabdomyoma

Smear with single large polygonal cells with abundant granular cytoplasm
Multiple eccentrically located nuclei with indistinct nucleoli
Intracytoplasmic cross striations seen in a minority of cells
No mitotic activity

Rhabdomyoma

Rhabdomyoma is a benign tumor with adult forms occurring almost exclusively in the head and neck region of older adults (295). Up to 20% can be multifocal. Cytologic smears demonstrate sparsely cellular specimens composed of large oval to round cell with abundant granular cytoplasm (Table 43). Occasionally, cross-striations may be seen. The differential diagnosis includes other neoplasms with granular cytoplasm including rhabdomyosarcomas, acinic cell carcinomas, paragangliomas, and granular cell tumors. Smears of acinic cell carcinomas are highly cellular with cohesive clusters of cells and contain many stripped nuclei in the background. FNAB smears from rhabdomyosarcoma demonstrate nuclear atypia and mitotic figures not seen in rhabdomyoma. IHC can help distinguish rhabdomyomas from granular cell tumors, as only the latter are S-100 positive (295).

Granular Cell Tumor

Granular cell tumor is a benign tumor of probable neural origin with a predilection for the head and neck region, with almost 50% occurring at this site, in particular, the larynx and tongue. FNAB smears are usually cellular with cells arranged in syncytial groups and lying singly (296). Cells demonstrate abundant granular cytoplasm and small bland round to oval nuclei. The differential diagnosis includes rhabdomyoma and rhabdomyosarcoma (discussed above), and alveolar soft part sarcoma (296). The latter demonstrates graded nuclear atypia and may show intracytoplasmic crystalloids.

C. FNAB of Selected Soft Tissue Sarcomas Encountered in the Head and Neck Region

Round Cell Sarcomas

Round cell sarcomas predominate in the pediatric age population with rhabdomyosarcoma being the most common extracranial soft tissue sarcoma occurring in the head and neck (Tables 40 and 44) (211,293,297). The International Classification of Rhabdomyosarcoma (ICR) recognizes five prognostically significant subtypes: spindle cell and botryoid embryonal (superior prognosis); embryonal (intermediate prognosis); and alveolar and undifferentiated (poor prognosis) (282,285,291). The various subtypes tend to predominate in different age groups and anatomic sites; therefore, clinical and radiographic correlation is essential. Most rhabdomyosarcomas occur in children younger than 10 years ; however, they can occasionally occur in adolescents and young adults. In general, when compared with the other round cell sarcomas,

Table 44 Key Diagnostic Features—Rhabdomyosarcoma

Alveolar rhabdomyosarcoma	Highly cellular smears Single cells and sheets of cells with fragile cytoplasm Majority cell population is a small early rhabdomyoblast with scant cytoplasm Variably sized nuclei with nuclear irregularities, coarse chromatin, and one or more nucleoli Multinucleated giant cells and strap cells characteristic
Embryonal rhabdomyosarcoma	Moderate to highly cellular smears Three cell types: early, intermediate, and late rhabdomyoblasts Predominant cell type is small with scant cytoplasm; secondary population of cells with more abundant cytoplasm Cytoplasmic vacuolization present Mitoses readily seen in most smears Round to oval eccentric nuclei with fine chromatin, nuclear irregularities, and variably sized nucleoli Background may be myxoid, tigroid, or contain necrosis

rhabdomyosarcoma tends to display more cytologic variability, especially in the embryonal subtype (Fig. 94 and 95). FNAB smears demonstrate cellular smears with predominantly discohesive cells of small to intermediate size and with round to ovoid hyperchromatic nuclei, and one or more prominent nucleoli. A fragile scant rim of cytoplasm, which can be easily stripped, is noted with many stripped nuclei present in the background. Occasional loosely cohesive groups of malignant cells can be seen. Cytoplasmic

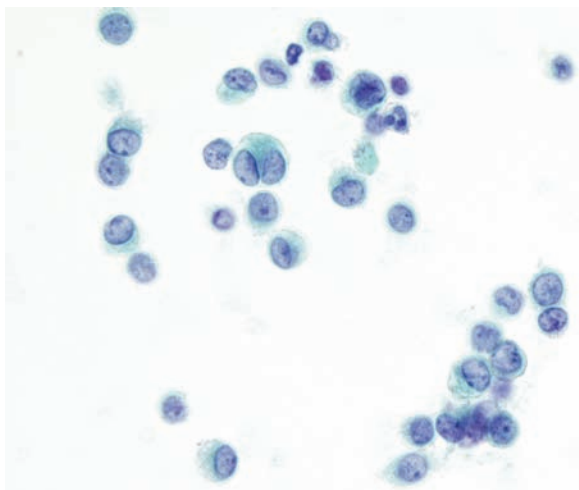


Figure 94 Embryonal rhabdomyosarcoma demonstrating a range of small to large tumor cells, some with binucleation, a feature helpful in differentiating from Ewing's sarcoma (Papanicolaou stain; magnification, 600×).

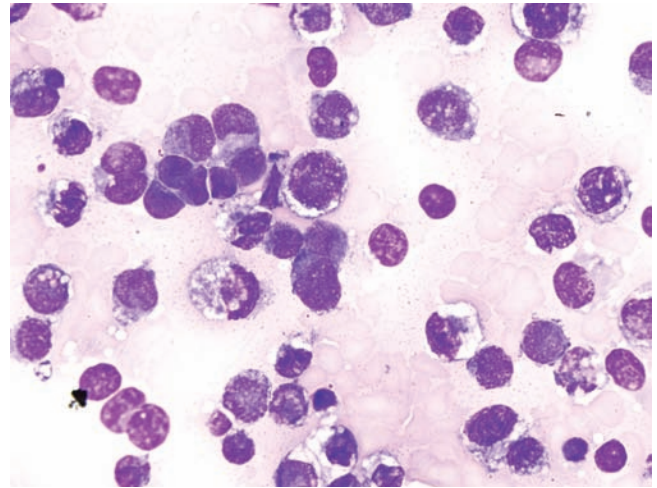


Figure 95 Compared with embryonal subtypes, the alveolar rhabdomyosarcoma has larger, more uniform rounded cells with hyperchromatic nuclei, one or more nucleoli, and a thin rim of cytoplasm. Vacuoles in the cytoplasm are seen in the majority of rhabdomyosarcomas (DQ stain; oil magnification, 600×).

vacuolization is noted in the majority of rhabdomyosarcomas; however, it is also commonly seen in Ewing's sarcoma and malignant lymphoma, which enter into the differential diagnosis (Fig. 95). A useful cytologic finding is the presence of binucleated and multinucleated cells, more often seen in the embryonal subtype (Fig. 94). IHC for myo-D1/myogenin, desmin, and actin are helpful in rendering a diagnosis of rhabdomyosarcoma. Cytogenetic studies demonstrate an 11q deletion and a 2;13 translocation in alveolar rhabdomyosarcomas (285).

Ewing's Sarcoma/PNET

Among round cell sarcomas, Ewing sarcoma/PNET is the most difficult to diagnose based solely on cytomorphology; however, ancillary studies can help to establish a diagnosis by FNAB. Aspirated specimens demonstrate highly cellular smears with strikingly uniform round cells with a very high nuclear/cytoplasmic ratio and cytoplasmic vacuoles and most cases also demonstrate pseudo-rosette formation (Fig. 96). Immunohistochemical staining for CD99 and FLI-1 can aid in the diagnosis and cytogenetic analysis for the t(11;22) reciprocal translocation has been successfully performed on aspirated material (285).

Polygonal/Epithelioid Cell Sarcomas

Polygonal/epithelioid cell sarcomas by definition represent high-grade sarcomas and include a diverse group of entities including epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma (melanoma of soft parts), and synovial sarcoma. Also included in the differential diagnosis of this subgroup is metastatic carcinoma and malignant melanoma as they commonly display an epithelioid morphology. The sarcomas

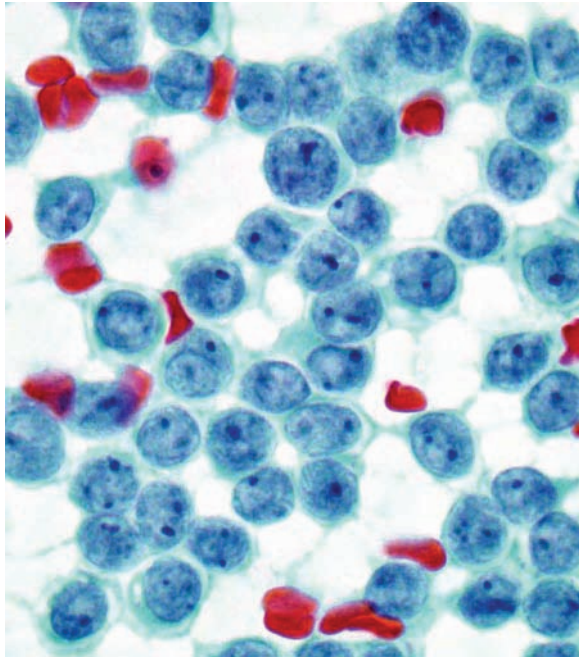


Figure 96 Aspirates from Ewing's sarcoma are highly cellular and contain a strikingly uniform population of cells with a very high nuclear-to-cytoplasmic ratio (Papanicolaou stain; oil magnification, 600 $\times$).

included in this group tend to affect adolescent and young adults and most often arise in the extremities, however, also tend to present with a high frequency of regional lymph node metastases that are highly uncommon in other soft tissue sarcomas. In such cases, exclusion of metastases from carcinoma and melanoma is necessary. Rendering a diagnosis of a polygonal/epithelioid sarcoma by FNAB without further subtyping can be adequate to initiate therapy as treatment for all sarcomas in this category is similar and includes both chemotherapy and adjuvant radiation therapy (298).

FNAB smears demonstrate cellular smears dominated by singly dispersed cells with a round/polygonal shape and moderate to abundant cytoplasm (Fig. 97). Nuclei tend to be eccentric and contain one or more prominent nucleoli. Bi- and multinucleated tumor cells can be identified in the smears. The cytomorphic features among entities in this group show considerable overlap; therefore, ancillary studies are generally needed to distinguish amongst them, but more importantly, to rule out a nonsarcomatous malignancy.

Synovial Sarcomas

Approximately 3% of synovial sarcomas occur in the head and neck region and have been reported in the larynx, hypopharynx, and retropharyngeal areas. They are of unknown histogenesis (299). Synovial sarcoma, with its biphasic morphology and immunohistochemical staining profile may be considered a “carcinosarcoma” of soft parts. FNAB smears from synovial sarcomas (monophasic and biphasic) demonstrate highly cellular

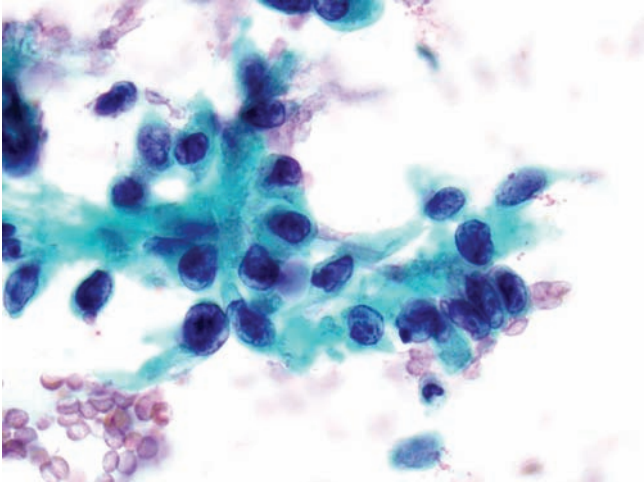


Figure 97 An aspirate from an epithelioid sarcoma with loose clustering of rounded to polygonal cells with eccentric nuclei, prominent nucleoli, and abundant cytoplasm (Papanicolaou stain; magnification, 600 $\times$).

Table 45 Key Diagnostic Features—Synovial Sarcoma

Cellular smears with cohesive clusters and single cells
Monomorphic population of round, ovoid, to occasionally spindled cells
Nuclei with fine granular chromatin and inconspicuous nucleoli
Few mitoses present

smears with predominantly discohesive cells and occasional loose cell aggregates (Table 45). Cells are generally uniform with round to ovoid to spindle cells, high nuclear to cytoplasmic ratios, small nucleoli, and scant to tapering cytoplasm (Fig. 98) (299). IHC plays a pivotal

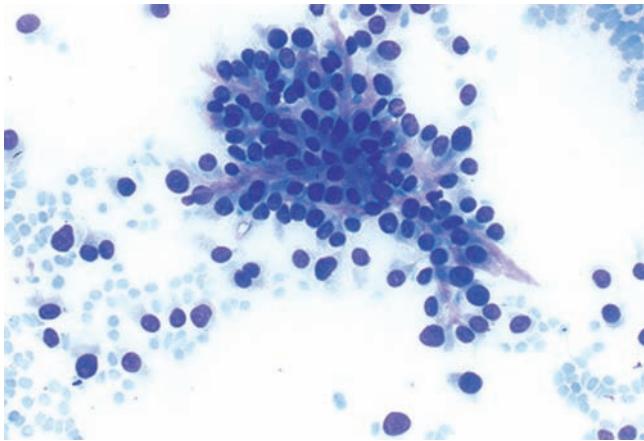


Figure 98 Monophasic synovial sarcoma showing uniform, round- to oval-shaped cells in a loose cluster. The cells have a high nuclear to cytoplasmic ratio, tapering cytoplasm, and inconspicuous nucleoli (DQ stain; magnification, 400 $\times$).

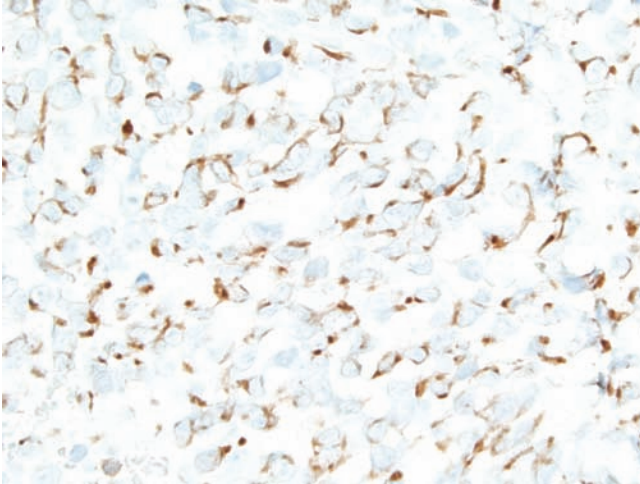


Figure 99 Immunostaining for pancytokeratin shows positivity within synovial sarcomas (immunohistochemical incubation for AE1/AE3 pancytokeratin marker; magnification, 400 $\times$).

role in the diagnosis of synovial sarcoma, which shows positive staining for cytokeratin, epithelial membrane antigen, and CD99 (Fig. 99). In addition, greater than 90% have the characteristic t(x; 18) translocation by cytogenetic analysis, which has been successfully performed on FNAB material (285).

Pleomorphic Sarcomas

Pleomorphic sarcomas are easily recognized as malignant and high-grade malignancies with moderate to highly cellular smears and predominantly dyscohesive cells and tumor giant cells. They tend to affect older adults (>50 years). Currently, all pleomorphic sarcomas (by definition, high-grade sarcomas) are treated similarly with surgical excision in most cases along with chemotherapy and/or radiation therapy. Therefore, histologic subtyping is not usually necessary and an FNAB diagnosis of “pleomorphic sarcoma, not otherwise specified” is generally sufficient to initiate appropriate therapy. Malignant fibrous histiocytoma (MFH) occurs in the sinonasal cavity and neck on rare occasions. MFH is best considered a generic high-grade sarcoma demonstrating a pleomorphic phenotype that can be more definitively classified with IHC and more reproducible diagnostic criteria as other more specific sarcomas, carcinoma, or melanoma (300). FNAB smears are generally highly cellular with marked nuclear pleomorphism, tumor giant cell formation, and variable cell morphology ranging from spindle to epithelioid shapes (Fig. 100). Differentiation from sarcomatoid carcinomas can be problematic. The presence of marked nuclear anaplasia and prominent numbers of anaplastic giant cells favors a diagnosis of MFH. However, most cases are best resolved by IHC for cytokeratins. Similarly, immunostaining for S-100, HMB-45, and Melan-A can confirm a diagnosis of malignant melanoma. Pleomorphic liposarcomas can be difficult to differentiate from

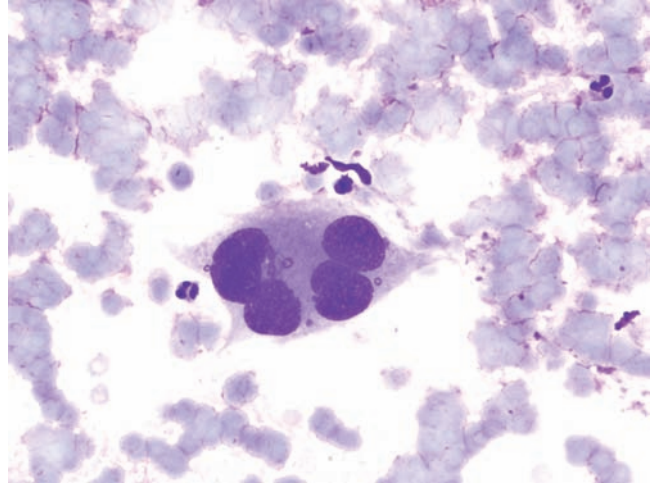


Figure 100 Aspirate from a malignant fibrous histiocytoma demonstrating a pleomorphic, multinucleated giant cell (DQ stain; oil magnification, 600 $\times$).

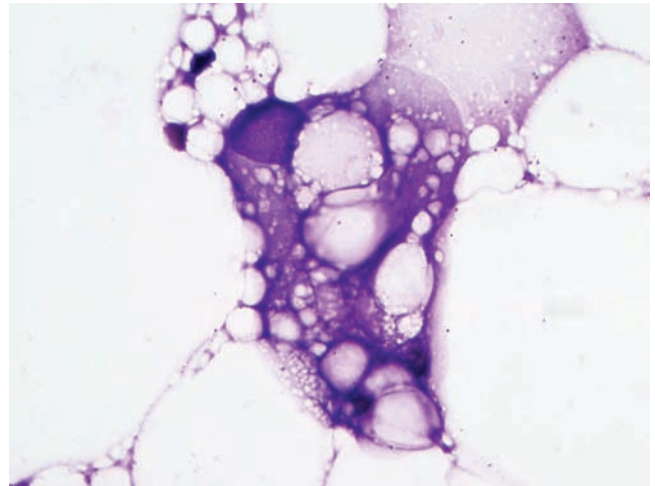


Figure 101 Aspirate from a pleomorphic liposarcoma with a classic lipoblast that shows an atypical and bizarre nucleus and abundant multivacuolated, lipid-laden cytoplasm (DQ stain; oil magnification, 600 $\times$).

MFH as both contain large numbers of anaplastic giant cells. Demonstration of lipoblasts, which may be rare or absent in an FNAB sample, is necessary for a definitive diagnosis of liposarcoma (Fig. 101) (301).

Osteosarcomas

Most osteosarcomas in the head and neck region occur in the jaw. Smears generally contain osteoid along with markedly pleomorphic ovoid to spindled cells with prominent nucleoli.

Spindle Cell Sarcomas

Spindle cell sarcomas include a broad group of tumors including synovial sarcoma (discussed under the epithelioid/polygonal sarcomas), malignant peripheral nerve sheath tumor (MPNST), leiomyosarcoma, fibrosarcoma, angiosarcoma, and some forms of MFH. In our experience and that of others, this group of lesions is the most diagnostically challenging by FNAB because of difficulties in accurately separating benign lesions from low-grade sarcomas and definitively classifying the sarcoma (302,303). Therefore, it is doubtful that spindle cell sarcomas can be accurately diagnosed by FNAB. Therefore, in this group of lesions, a CNB may be the preferred diagnostic modality (211).

Leiomyosarcomas

Leiomyosarcomas occur in the superficial soft tissues of the head and neck and the low-grade leiomyosarcomas are aspirated most often. FNAB smears demonstrate low to moderate cellularity with a predominance of cohesive cell clusters arranged in parallel bundles and containing characteristic cigar-shaped nuclei (Fig. 102). High-grade lesions demonstrate increasing nuclear pleomorphism, prominent nucleoli, and background necrotic debris. The high-grade pleomorphic leiomyosarcomas may be difficult to separate from other adult pleomorphic sarcomas; however, treatment is essentially similar and an FNAB diagnosis of “pleomorphic sarcoma, not otherwise specified” would be enough to initiate appropriate therapy. Low-grade leiomyosarcomas may be impossible to separate from leiomyomas, however, the presence of atypia and mitoses would support a leiomyosarcoma diagnosis (291,303). Immunohistochemical staining with muscle markers (i.e., desmin, muscle specific

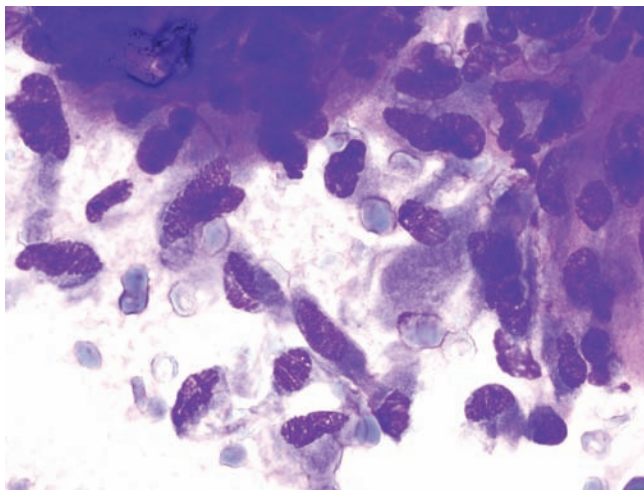


Figure 102 Cellular aspirate from a leiomyosarcoma composed of cohesive clusters of tumor cells with variable pleomorphism, cigar-shaped nuclei, and tapering cytoplasm (DQ stain; magnification, 600 $\times$).

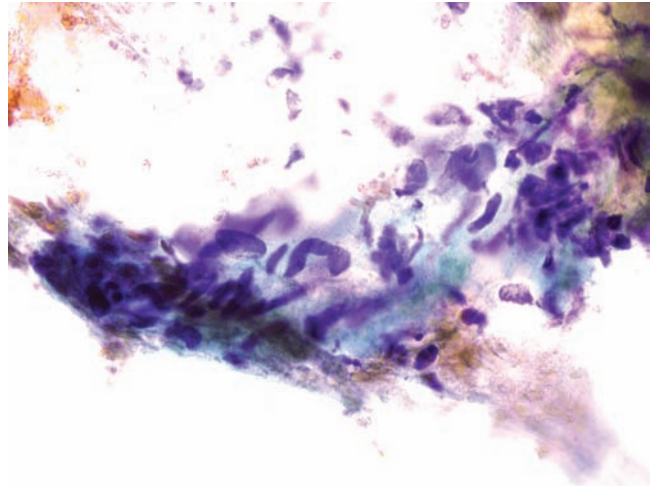


Figure 103 Singly dispersed and loosely clustered malignant cells from a malignant peripheral nerve sheath tumor with characteristic comma- to serpentine-shaped cells with hyperchromatic nuclei and variable tapering cytoplasm (DQ stain; magnification, 600 $\times$).

actin, caldesmin) can help to separate leiomyosarcomas from other spindle cell sarcomas.

FNAB smears from MPNST demonstrate obvious malignant features with moderate to highly cellular smears containing a predominance of single cells and some loosely cohesive clusters of malignant cells. The characteristic wavy, bent-shaped nuclei with hyperchromasia, irregular nuclear membranes, and high nuclear/cytoplasmic ratios are evident and mitoses can be seen with higher-grade lesions (Fig. 103) (302). IHC can be useful in separating MPNST from leiomyosarcoma (muscle markers), synovial sarcoma (cytokeratin and epithelial membrane antigen), and MFH. The most useful finding for making a correct diagnosis is the clinical scenario for diagnosing a high-grade MPNST with a history of preexisting neurofibroma, neurofibromatosis, and origin from a major nerve trunk (211,291).

Myxoid Soft Tissue Sarcomas

Myxoid soft tissue sarcomas are lesions that, by definition, display myxoid morphology as a dominant feature. In our experience, the most commonly sampled myxoid sarcomas by FNAB are myxoid liposarcoma, myxofibrosarcoma (myxoid MFH), and extraskeletal myxoid chondrosarcoma. The FNAB findings of these lesions have been previously well described (291,303–306).

Myxoid liposarcomas. Myxoid liposarcomas are low-grade sarcomas and are the most common malignant lipomatous tumor in adults, affecting patients aged between 40 and 70 years. These lesions can occur at almost any site but are most common in the deep soft tissues. FNAB smears demonstrate variable numbers of myxoid stromal fragments, plexiform or “chicken wire” vascular pattern (best seen on cell

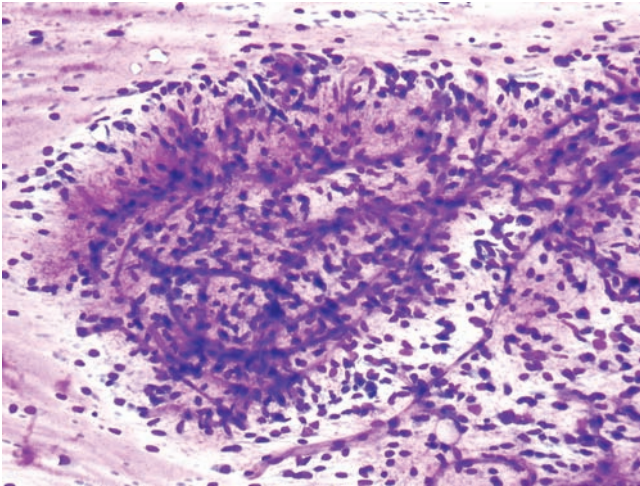


Figure 104 Aspirate from a myxoid liposarcoma composed of a vascular network in a myxoid stroma. The vascular channels are surrounded by atypical spindled cells (DQ stain; magnification, 600 $\times$).

block material), and uniform mononuclear cell population of oval to spindle cells as well as with variable numbers of univacuolated lipoblasts (Fig. 104). The presence of lipoblasts is the only significant feature for rendering a diagnosis of myxoid liposarcoma (304). Lipoblasts must be searched for carefully as they are not a dominant feature seen on most FNAB smears.

VI. ORAL CAVITY

A. Introduction

Annually, there are approximately 19,000 new cases of oral cavity cancers in the United States, accounting for 4% of all new malignancies. Most of these cases present in a late stage (307,308). Open surgical biopsy is the standard procedure for the diagnosis of suspicious lesions of the oral cavity, although cytologic examination of surface scrapings has been used for the diagnosis of dysplastic or neoplastic changes. However, a high false-negative rate was reported in several studies (309–311). In addition, exfoliative cytology has been found not to be practical for non-epithelial or submucosal lesions. In contrast, FNA has been shown to be a reliable and safe technique for the diagnosis of malignancy in oral and pharyngeal lesions (312,313) and provides an alternative to open biopsy with few false-negative cases (314,315). FNA is especially useful in deep-seated extranodal or glandular masses covered with intact mucosa. In these instances, the needle usually has to be directed with imaging techniques (316).

B. Benign Oral Lesions

Benign oral lesions have variable clinical appearances that often make diagnoses difficult. Many of these

lesions are initially examined with cytologic scrapings in an attempt to differentiate them from malignant lesions. Smears from buccal mucosa may show enlarged nuclei in patients with pernicious or iron deficiency anemias (317). Similar cytologic changes can also be seen in patients who are receiving certain drugs, irradiation treatment, or chemotherapy.

Ulcerations and Inflammatory Conditions

Regenerative and/or degenerative cellular changes associated with acute and/or chronic inflammation can be seen in a wide range of infectious diseases. Scrapings from these lesions may reveal parabasal-like cells with enlarged nuclei and scanty surrounding cytoplasm. Infrequently, prominent and multiple nucleoli, abnormal chromatin patterns, and multinucleation are seen. These findings can simulate malignant-appearing cells; however, false-positive results are infrequent when examination is performed by experienced cytopathologist.

Oral radiation for cancer induces numerous cytologic changes that may persist for long periods after completion of the therapy. These changes include nuclear and cytoplasmic enlargement, vacuolation, binucleation, and nuclear aberrations (318).

Candida albicans pseudohyphae and spores are best seen in scrape smears from whitish areas on the oral mucosa. The infection and organism load is commonly very intense in patients with immunosuppression, such as HIV-positive patients (318).

Primary herpetic stomatitis. Primary herpetic stomatitis is an acute oral herpesvirus infection characterized by crusting of the lips, painful single or multiple mucosal ulcers, associated with lymphadenopathy and fever. Scraping cytology shows bizarre multinucleated syncytial giant cells with molded nuclei, beaded nuclear membranes and intranuclear inclusions or clear “ground glass” nuclei in Papanicolaou-stained smears (318) (Fig. 105). The common recurrent aphthous ulcer (canker sores) is not due to the herpesvirus and usually demonstrates slightly enlarged nuclei with surrounding acidophilic cytoplasm (318,319).

Pemphigus vulgaris. The mucosa of the mouth is usually involved in *pemphigus vulgaris* and may be the initial finding. The type and appearance of the oral lesions are similar to those of the skin. Acantholytic changes are characterized by numerous uniform basal and parabasal cells with increased nuclear to cytoplasmic ratios and large single or multiple irregular nucleoli (320). Perinuclear cytoplasmic halo formation may be seen. The cells may be mistakenly interpreted as suspicious for malignancy.

Mucous retention cysts. Mucous retention cysts or ranulas represent dilated ducts or collections of extravasated mucous arising in association with minor salivary glands and most often occur in the lower lip (321). Aspiration of these lesions will yield a small amount of gray to white clear mucoïd material. In general, the aspirate is extremely hypocellular with only scattered histiocytes.

Leukoplakia. Leukoplakia may be defined as any white plaque that cannot be scraped from the oral

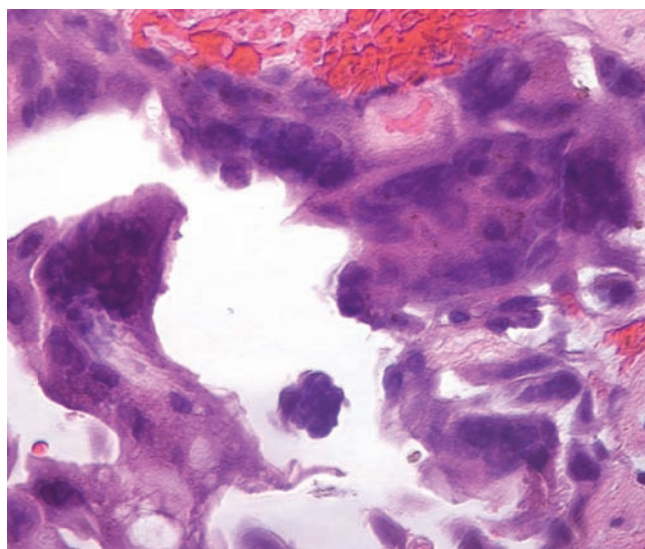


Figure 105 Oral herpetic ulcers. Scraping cytology shows giant cells with multinucleation, molded nuclei, beaded nuclear membranes, and clear “ground glass” nuclei. (H&E stain; magnification, 600×).

mucosa. An erythematous component increases the risk of dysplasia or carcinoma (322). Cytopathology smears from the surface may yield dysplastic cells. Presence of any cytologic atypia requires a biopsy specimen (318,323) (Fig. 106). EBV appears to be a cofactor in the oral hairy leukoplakia associated with HIV infection. Oral hairy leukoplakia presents primarily on the lateral tongue as a corrugated or hair-like white lesion. The definitive diagnosis is established by biopsy specimens, in which koilocytes and hyperkeratosis are seen (323).

Rhabdomyoma. Rhabdomyoma is a rare benign tumor of skeletal muscle origin, found most frequently

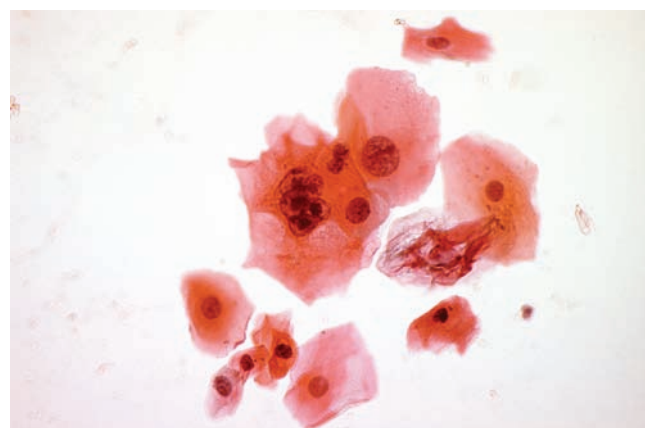


Figure 106 Leukoplakia. Scrape cytology smear from the leukoplakia surface yields dysplastic cells. Tissue biopsy shows carcinoma in situ (Papanicolaou stain; magnification, 400×).

Table 46 Key Diagnostic Features—Granular Cell Tumor

Cellular smears with dissociative cell pattern
Abundant granular cytoplasm with low nuclear to cytoplasmic ratio, stains deep blue in Diff-Quik stain
Small, round and bland nuclei
Mitosis and necrosis can be seen in malignant tumors

in oral cavity. Adult rhabdomyoma is the most common type. The cytologic features have been infrequently reported in the literature (324–326). The aspiration smears and cytopsin preparations contain clusters of large polygonal cells with abundant granular cytoplasm with indistinct borders and uniform, peripherally located nuclei that are rarely multiple. Occasionally, cross-striations are identified in the cytoplasm on Papanicolaou and DQ stains, but are more prominently seen in the cell block hematoxylin and eosin preparations. Nuclear atypia and mitotic figures are absent (324–326).

Granular cell tumor. Granular cell tumor is a benign neoplasm of probable neural origin, especially involving the larynx and tongue in the head and neck region. As the name implies, these neoplasm are composed of large cells with abundant granular cytoplasm. The smears are generally highly cellular with single cells or syncytial groups (327) (Table 46). The nuclei are usually small, round, and bland, but can show considerable pleomorphism. Nucleoli are indistinct. The cytoplasm is abundant, granular, and stains deep blue in DQ preparation (Fig. 107). The granules within the cytoplasm stain positively with the periodic acid-Schiff (PAS) stain. The cells are fragile and nuclei are frequently stripped from the cytoplasm, imparting a granular background with a “dirty” appearance (328,329). Hyperchromasia, increased nuclear to cytoplasmic ratios, coarse chromatin, numerous mitosis, vesicular nuclei with enlarged nucleoli, spindle cell morphology, and increased proliferative activity evaluated by IHC are associated with malignancy (328). Some authors caution that identification of mitosis

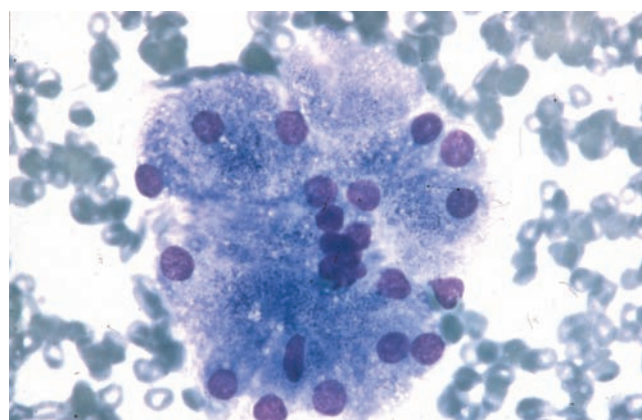


Figure 107 Granular cell tumor. FNAB shows dyscohesive single cells, with small, round, bland nuclei, and indistinct nucleoli. The cytoplasm is abundant, granular and stains deep blue in DQ preparation (DQ stain; magnification, 400×).

and necrosis is needed before rendering a malignant diagnosis (330).

Epithelioid hemangioendothelioma. Epithelioid hemangioendothelioma is a rare vascular neoplasm with a biological behavior intermediate between hemangioma and angiosarcoma (331). Only a few cases have been reported in the oral cavity, with a wide distribution of patient ages and female predominance (332). The sites of the tumor include the tongue, lip, jaw, buccal mucosa, and the floor of the mouth. A painless solitary mass is the most common presentation (332).

The smears are usually sparsely cellular consisting of predominantly single, large polygonal cells in a bloody background. A few atypical cells embedded in a dense metachromatic stroma can be seen. These atypical cells have abundant dense or fine granular cytoplasm with ill-defined cell borders. The nuclei are enlarged, oval, and eccentrically located, with fine chromatin and indistinct nucleoli. Some binucleated and multinucleated cells can be present. Characteristically, some cells show large cytoplasmic vacuoles compressing the nuclei, some of which contained degenerated RBCs. Intranuclear inclusions are seen and considered to be the most reliable diagnostic feature in FNAB (333–335). Distinction between epithelioid hemangioendothelioma and epithelioid angiosarcoma may be difficult. However, significant cytologic atypia, nuclear pleomorphism, brisk mitotic activity, and necrosis favor a diagnosis of epithelioid angiosarcoma (336). Epithelioid sarcoma usually occurs in the distal upper extremities of young adults (332). Aspirates are hypercellular and composed of both cellular aggregates and isolated tumor cells. Epithelioid sarcoma is positive for vimentin and cytokeratin and is negative for vascular markers such as factor VIII, CD31 and CD34, in contrast to epithelioid hemangioendothelioma (330–332).

Epithelioid hemangioma. Epithelioid hemangioma is a benign vascular tumor rarely seen in the oral cavity (337). It usually presents as a small (< 3cm), red or brown, circumscribed mass, and composed of lobular proliferation of vascular like channels lined with plump endothelial cells (337). The vascular proliferation is associated with infiltration of lymphocytes, plasma cells, and abundant eosinophils. On FNA, the neoplastic cells may be spindle or polygonal (338). The nuclei are bland and usually oval with smooth nuclear contours and vesicular chromatin. The cytoplasm is granular and eosinophilic, but lacks the dense texture of hemangioendothelioma cells. In addition, most of the neoplastic cells form cohesive and vascular-like cell aggregates with only a few single neoplastic cells in the background. Inflammatory components, particularly eosinophils are present in aspirates of epithelioid hemangioma, but are not seen in epithelioid hemangioendothelioma (338).

Teratoid cysts. Teratoid cysts consist of three distinct histological types: epidermoid (simple), lined by stratified squamous epithelium without dermal appendages; dermoid (compound), consisting of typical squamous epithelium and dermal appendages such as hair, hair follicles, and sebaceous and sweat glands; and teratoid (complex), consisting of tissues

from all three germ layers such as respiratory, intestinal, and nervous system (339). The lumen of all three types of dermoid cyst displays a greasy, cheese-like, white gray or yellow tan content, formed by shed keratin and sebaceous material (340–342). When lined by squamous cells, differentiation between a thyroglossal duct cyst, branchial cleft cyst, and teratoid cyst can be difficult (342).

C. Malignant Oral Lesions

Squamous Cell Carcinoma

Oral squamous cell carcinoma is the most common oral lesion to be sampled by swab and/or scrape smears (318). Prior scrape or aspiration cytology of an indurated, raised, or ulcerated intraoral lesion, combined with aspiration of any associated cervical lymphadenopathy will establish the diagnosis in the majority of cases. In the absence of metastatic disease, scrape cytology cannot reliably separate in situ from invasive squamous tumor. In this instance, biopsy may be recommended.

Squamous cell carcinoma is divided into keratinizing and nonkeratinizing types (318,343). Cytologic features of keratinizing squamous cell carcinoma is characterized by cellular smears in which numerous dispersed anucleated keratinized squames and keratinized nucleated cells (Fig. 108). The smears contain many single cells and clusters of neoplastic cells are present. The individual cells have abundant pink to orange dense cytoplasm. Squamous pearls are often seen. When keratin debris is abundant, foreign body giant cells may be present. Moderately and poorly differentiated squamous cell carcinomas demonstrate little evidence of keratinization consisting of individual

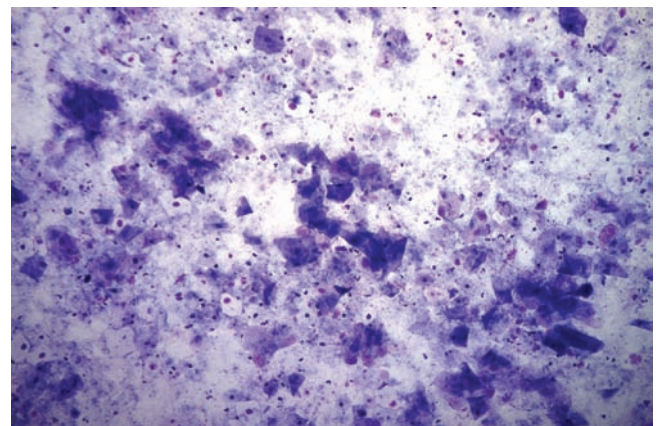


Figure 108 Well differentiated keratinizing squamous cell carcinoma. Smears are characterized by high cellularity with abundant anucleated and nucleated keratinized squamous cells. Differentiating reactive atypia in branchial cleft cyst from well-differentiated squamous cell carcinoma can be challenging. Features supporting the branchial cleft cyst include numerous anucleated squames and prominent acute inflammation (not seen in this smear) (DQ stain; magnification, 200×).

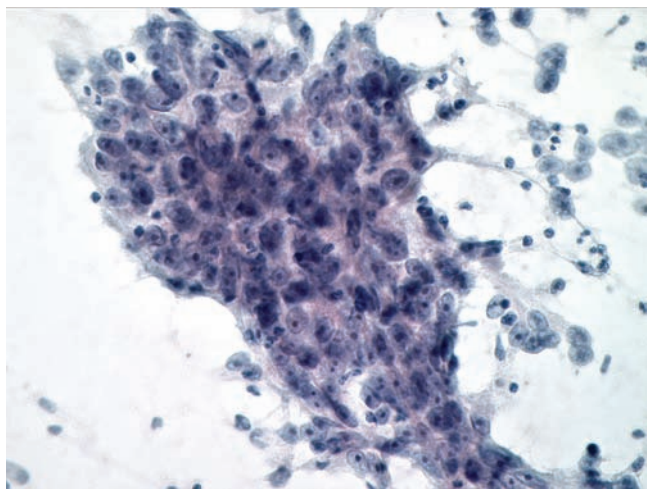


Figure 109 Poorly differentiated squamous cell carcinoma. Smears show cohesive and dyscohesive group of cells with vesicular nuclei, coarsely granular chromatin, and large prominent nucleoli. No evidence of squamous keratinization is seen in the specimen (Papanicolaou stain; magnification, 400×).

cells or clusters with indistinct cytoplasmic margins and large nuclei with irregular nuclear membranes. Squamous cell carcinomas usually have hyperchromatic, clumping to dense or opaque nuclei. In poorly differentiated squamous cell carcinoma, vesicular nuclei with coarsely granular chromatin and large prominent nucleoli are seen (Fig. 109). Mitotic figures are numerous (344).

Basaloid squamous cell carcinoma. The basaloid variant of squamous cell carcinoma is a highly malignant neoplasm, frequently presenting with metastatic disease at the time of diagnosis. Metastatic deposits may consist of basaloid and/or squamous carcinoma cells. Basaloid squamous cell carcinoma has a distinctive cytological pattern characterized by occasional sheets of cohesive neoplastic cells with high nuclear to cytoplasmic ratios and hyperchromatic nuclei that can occasionally mimic small cell carcinoma (345) (Fig. 110A, Table 47). Smears of the aspirate show a mixed lymphoid background with interspersed cohesive clusters of small cells. The cells are generally hyperchromatic with evenly staining dense chromatin or irregularly distributed coarse chromatin. In contrast to small cell carcinoma, nucleoli are usually evident (Fig. 110B). On DQ staining, irregular globules of magenta-stained extracellular dense material within or adherent to the periphery of some clusters can be seen. Abundant mitotic figures and necrosis are often present. IHC is useful since basaloid squamous carcinoma is positive for high-molecular weight cytokeratin, p63, and CK5/6, but negative for TTF-1, CK7, and neuroendocrine markers (345,346).

There are several diagnostic problems and pitfalls in the interpretation of FNA of squamous cell carcinoma, including cystic changes, well-differentiated and spindle squamous cell carcinomas, foreign-body

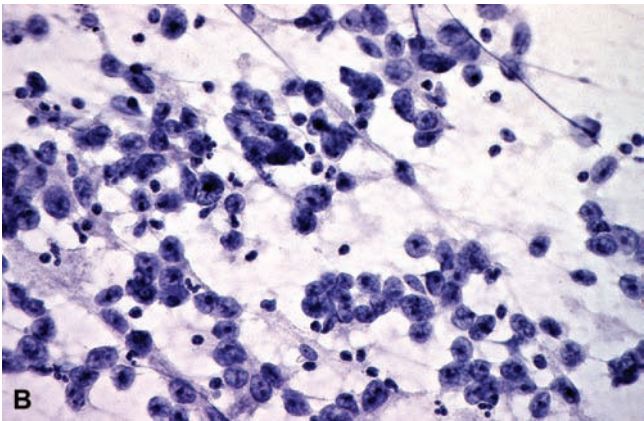
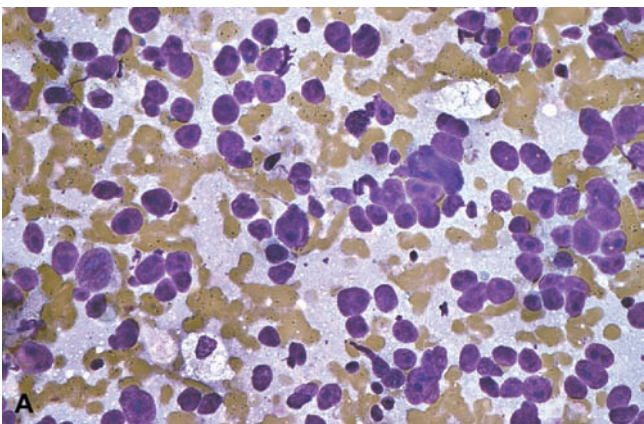


Figure 110 Basaloid squamous cell carcinoma. (A) Smears are characterized by dyscohesive neoplastic cells with high nuclear to cytoplasmic ratio, hyperchromatic nuclei, mimicking small cell carcinoma. (B) In contrast to small cell carcinoma, large nucleoli are evident [(A) DQ stain; magnification, 400× (B) Papanicolaou stain; magnification, 400×].

Table 47 Key Diagnostic Features–Basaloid Squamous Cell Carcinoma

Dyscohesive cells with high nuclear to cytoplasmic ratio
Hyperchromatic nuclei with occasional molding
Prominent nucleoli (in contrast to small cell carcinoma)
Magenta stained extracellular dense material within or adherent to the malignant cell clusters.

giant cells reaction, keratin plaques, and ghost cells. Recognition of these patterns along with clinical correlation enables the pathologist to prevent a false-negative diagnosis (347).

Metastatic squamous cell carcinoma. Metastatic squamous cell carcinoma should be differentiated from branchial cleft cyst (Fig. 108). Branchial cleft cyst occurs in the lateral neck along the anterior border of the sternomastoid muscle forming a soft to firm nodule. Smear preparations show large number of anucleated keratinizing squamous cells, with some squamous cells showing varying degrees of maturation (348,349). The background is granular with

amorphous debris and frequently contains neutrophils. Squamous cell nuclei can show reactive atypia and can be a pitfall for squamous cell carcinoma. Increased nuclear to cytoplasmic ratios, irregularity of nuclear outline, and nuclear hyperchromatism are characteristics for squamous cell carcinoma. In addition, the background of squamous cell carcinoma contains more necrotic debris and fewer polymorphonuclear cells than aspirates of benign cysts. However, well-differentiated squamous cell carcinoma can have minimal atypia while branchial cleft cysts can show significant inflammatory atypia, making the distinction more challenging (Fig. 5). In such situations, excision biopsy is highly recommended, especially in older patients.

Aspirates from midline thyroglossal duct cysts may be indistinguishable from branchial cleft cysts. Cytomorphologic features are not unique; therefore, clinico-radiologic correlation should lead to the correct diagnosis. Abundant colloid, most often with ciliated columnar epithelium, is the predominant cytopathologic finding (349).

Salivary Gland Lesions

Tumors of the minor (accessory) salivary glands most commonly occur as nodular or ulcerative lesions in the tongue, hard palate, or buccal mucosa. Minor salivary tumors are commonly malignant such as mucoepidermoid, adenoid cystic, and PLGA (Table 48). FNA of salivary gland neoplasms are discussed in detail elsewhere in this chapter.

PLGA. PLGA is a rare neoplasm that occurs almost exclusively in the minor salivary glands, particularly in the palate (350). This tumor is a low-grade malignancy that infrequently metastasizes to regional lymph node and rarely metastasizes to lung (350). FNA shows hypercellular smears with numerous epithelial cells in a blood-stained background. The cells are mostly arranged in branching papillae, sheets, and clusters composed of bland, relatively uniform cells. The cells are cuboidal in shape, with mild atypia. The nuclei are enlarged, round to oval, moderately hyperchromatic in shape, with coarsely granular, dispersed chromatin, and absent or inconspicuous nucleoli. The cytoplasm is moderate, dense, basophilic, with indistinct borders (351–354). Bare nuclei also frequently appear in the background. Myxoid matrix, either dispersed in the background or interspersed with the cellular elements, is also seen often.

The differential diagnosis includes ACC, mucoepidermoid, monomorphic adenoma, and pleomorphic adenoma. However, absence of squamous cells and extracellular or intracellular mucin should exclude mucoepidermoid. The absence of three-dimensional cell clusters with a central core of hyaline basement

membrane-like material should exclude ACC. PLGA should not be confused with SDC, which is a high-grade and clinically aggressive tumor showing considerable cellular pleomorphism, anisonucleosis, and tissue fragments with a cribriform pattern (355).

Nonepithelial Tumors

Nodal and extranodal lymphoma. Primary intraoral and perioral, localized nodal, and extranodal lymphoma forms a considerable proportion of all lymphomatous presentations. We recommend that the initial investigative biopsy should be FNAB. The diagnosis of lymphoma requires recognition of cell type with appropriate application of immunostaining/or flow cytometry to define the immunophenotype (318,322).

Kaposi's sarcoma. In AIDS patients, Kaposi's sarcoma commonly presents with nodular orofacial masses without ulceration and is especially seen involving the palate (356). There may or may not be accompanying lymphadenopathy (318,356). Aspiration cytology usually produces a hypocellular specimen. However, the diagnosis may be more readily made when lymph nodes are involved (357,358). If cellular, the aspirate shows tangles and individually dispersed cells. The cells are spindle or polygonal cells with bland, plump nuclei without hyperchromatism, and occasionally reveal characteristic longitudinal nuclear grooves (356). Hemosiderin granules may be found in accompanying macrophages. The most characteristic cytologic features are intact tissue fragments composed of overlapping spindle cells with nuclear distortion and ill-defined cytoplasmic borders. Smaller groups of loosely cohesive spindle-shaped cells and individual spindle cells with cytoplasm can also be helpful features (356). Radial arrangement and nuclear crush artifacts have not been described in other spindle-cell intranodal lesions that could be considered in differential diagnoses (51). Spindle cells are usually positively immunostained for factor VIII, CD34, CD31, and vimentin and negative for S-100, alpha-smooth muscle actin (α -SMA), and desmin.

Neurofibroma. Occasionally, neurofibroma occurs in the tongue and may be diagnosed by FNA biopsy. The appreciation of microtissue fragments of thin spindle cells with wavy spindle nuclei along with loosely cohesive and individual scattered spindle cells are seen (321). Often intermingled mast cells are present in the background.

Sarcomas. Chondrosarcoma, osteosarcoma, rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, and angiosarcoma may all present as primary tumors in the soft tissues and bone of the oral cavity. The cytologic findings are variable depending on the type of sarcoma with features comparable to soft tissue malignancies at other sites. Complete discussion of the FNA cytology features of sarcoma has been previously presented in this chapter.

Table 48 Differential Diagnosis of Minor Salivary Gland Tumors Arising in Oral Cavity

Pleomorphic adenoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma (PLGA)

VII. NASAL CAVITY AND PARANASAL SINUSES

A variety of benign and malignant lesions affect the nose, paranasal sinuses, and facial bones. The parapharyngeal space is a well-defined anatomic zone of

loose connective tissue lying deep to the tonsil and lateral to the pharynx. Rare neoplasms arising within the parapharyngeal space are salivary gland tumors, squamous-cell carcinomas, adenocarcinoma, lipoma, neurofibroma, paraganglioma, schwannoma, chordoma, and NHL (359).

A. Benign Lesions

Paranasal Sinus Mucocoeles

Paranasal sinus mucocoeles are cystic expansions of the paranasal sinuses due to obstruction of the draining ostia. Aspiration of these masses will yield thick clear white mucus, which contains foamy or vacuolated mucus-filled histiocytes (321). In long-standing cases, the surrounding bone may show radiologic evidence of resorption.

Rhinoscleroma

Rhinoscleroma is a chronic granulomatous disease caused by the Gram-negative bacteria, *Klebsiella pneumoniae rhinoscleromatis*, occurs most frequently in the middle East, Africa, and South America, and primarily involves the nasal cavity and nasopharynx (343). Cytologic examination shows granulomatous inflammation in which foamy macrophages (Mikulicz cells) are admixed with plasma cells and granular histiocytes (360). These macrophages contain short rod-shaped organisms with thick capsules and bipolar cytoplasmic enlargements, best identified with Warthin-Starry stain (361).

Myospherulosis

Myospherulosis usually follows nasal surgery and packing of the area with petroleum-impregnated gauze (362–364). A chronic inflammatory infiltrate surrounds spaces within a fibrotic stroma. Lying free within the spaces are saclike structures called “parent bodies,” which contain many spherules.

Smears contain large numbers of spherules measuring between 4 and 7 μm in diameter, best seen in Papanicolaou stain (362). They have smooth distinct borders and contain discrete internal bodies that may be single and central with a halo or multiple attached to the periphery of the large spheres (362,363). The spherules are orange to green. Myospherulosis must be distinguished from fungal infections. However, fungal culture and stains are negative.

Angiofibromas

Angiofibromas occur almost exclusively in young adult men. It may be hormonally-induced, secondary to imbalance between estrogen and testosterone levels (365). Most angiofibromas arise along the lateral or superior nasopharyngeal wall and associated with local destruction. Angiofibromas manifest with unilateral nasal obstruction, epistaxis, facial swelling, exophthalmos, diplopia, or headache (366). Clinically, the tumor is lobulated, sessile, red to tan, filling the nasopharynx (366). Cytologic findings are variable,

but smears are usually very bloody (323,343). Plump spindle-shaped cells with pale indistinct cytoplasm are admixed with blood cells. The nuclei are bacillary shape with blunt ends and a few nuclei may have folds or bends in their nuclear membranes. The chromatin is finely granular and small, but distinct nucleoli may be present.

Angiofibromas can be distinguished from nerve sheath tumors and malignant vascular neoplasms by their location and clinical features. Vascular malignancies generally have a population of plumper cells with more nuclear atypia (367).

Sinonasal Hemangiopericytoma (Solitary Fibrous Tumor)

Approximately 20% of hemangiopericytomas are found in the head and neck, especially the nasal cavity and paranasal sinuses. Histologically, the tumor is circumscribed and composed of tightly packed proliferation of short spindle or oval cells that form arcades around vascular slits and spaces lined by endothelial cells (368). Reticulin stains demonstrate reticulin fibers around each pericyte.

The cytologic smears are modestly cellular with bloody background (368). The cells usually form tight aggregates and run in bundles, often with an arching appearance. Individual cells are oval or short spindle-shaped and radiate along the long axis of the bundles. The nuclei are bland, uniform, and oval, with finely granular chromatin and inconspicuous nucleoli. No mitotic figures or necrosis are identified. The presence of branched capillaries and abundant basement membrane material supports a diagnosis of hemangiopericytoma (368). Malignant hemangiopericytoma demonstrates uninuclear tumor cells with high nuclear to cytoplasmic ratios, evenly distributed chromatin and one or two small but distinct nucleoli (369).

B. Malignant Lesions

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma is a relatively uncommon malignancy in western counties, but frequently seen in China. It can be classified into keratinizing, non-keratinizing, and undifferentiated types. The neoplasms may present as a neck mass, with hearing loss, nasal obstruction, nasal discharge, headache, or bleeding (343).

Metastasis to neck lymph nodes often is the initial presenting sign of occult head and neck carcinomas, including undifferentiated nasopharyngeal carcinoma (370). Cytologic findings from metastatic deposits have been reported (370–373). Cytologic findings in FNA obtained from the keratinizing and non-keratinizing subtypes of nasopharyngeal carcinoma resemble squamous cell carcinoma arising at other sites. The aspirates of undifferentiated nasopharyngeal carcinoma are more unique. These smears are highly cellular and show clusters of cohesive neoplastic cells with sharp or irregular edges, along with numerous single neoplastic cells (Fig. 111). The nuclei of the neoplastic epithelial cells are oval or spindle-shaped, with hyperchromatic nuclei and prominent

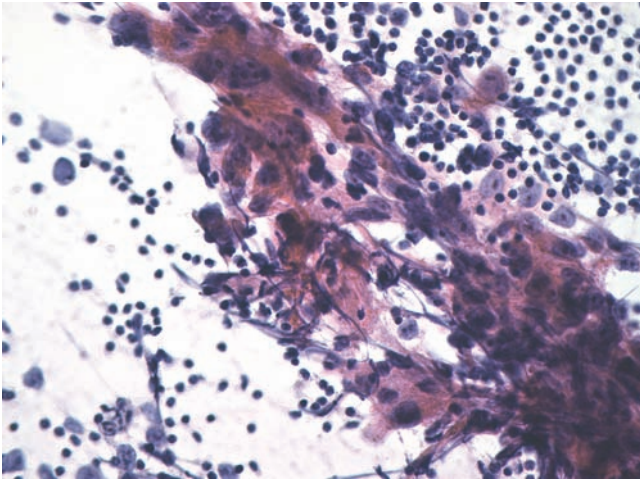


Figure 111 Undifferentiated nasopharyngeal carcinoma. FNAB smears are cellular and show clusters of cohesive neoplastic cells with sharp or irregular edges, along with numerous single neoplastic cells. The nuclei of the neoplastic epithelial cells are oval or spindle-shaped, with hyperchromatic nuclei and prominent nucleoli. (Papanicolaou stain; magnification, 400 $\times$).

nucleoli. Mitotic figures are frequent. The cytoplasm is generally pale, with ill-defined borders. Mature lymphocytes are intermingled with tumor cells in all cases (370).

It is frequently difficult to separate undifferentiated nasopharyngeal carcinoma from lymphoma. Recognition of cohesive cell clusters supports the epithelial nature of the tumor cells, along with positive staining for cytokeratins. In addition, the nuclei of nasopharyngeal carcinoma are more vesicular and have a more oval or spindle shape than nuclei seen in lymphoma (371).

EBV infection is consistently associated with undifferentiated nasopharyngeal carcinoma and can be detected using a nonradioisotopic in situ hybridization assay in FNA specimens. Therefore, detection of EBV may be successfully used to identify the nasopharyngeal origin of metastatic undifferentiated carcinoma (374,375).

Olfactory Neuroblastoma (Esthesioneuroblastoma)

Olfactory neuroblastoma (esthesioneuroblastoma) is a rare tumor of neuroectodermal origin that was first described by Berger and Richard in 1924 (376). Olfactory neuroblastoma constitutes approximately 0.3% of upper aerodigestive tract malignancies and 6% of nasal cavity and paranasal sinus tumors (377). The majority of patients are young adults, presenting with unilateral nasal obstruction or epistaxis.

FNA of olfactory neuroblastoma is infrequently encountered and is limited to case reports or small series in the literature (378–383) (Table 49). Aspirates from olfactory neuroblastoma are generally cellular and bloody with many isolated round cells and small clusters of round cells (381–383). Two cell-population

Table 49 Key Diagnostic Features—Olfactory Neuroblastoma

Cellular smears with dispersed cell pattern and small clusters of round cells
Rosettes formation with open central lumen or core containing blood vessels (infrequently seen)
Distinct fibrillary appearance in cytoplasm and fibrillary material in the background
Paranuclear “blue bodies,” minimally indent the nuclei or seen in the cytoplasm of macrophages.
Nuclei with coarse granular chromatin and single or multiple nucleoli
Tumor necrosis with dirty background

of intact viable cell nuclei and pyknotic nuclei are seen. The clusters show marked nuclear overlapping. Rosette structures are found with open central lumens or cores containing blood vessels. Fibrillary background material is seen. The nuclei are uniform, round or oval, with dark condensed chromatin and one to two nucleoli (Figs. 112 and 113). Nuclear

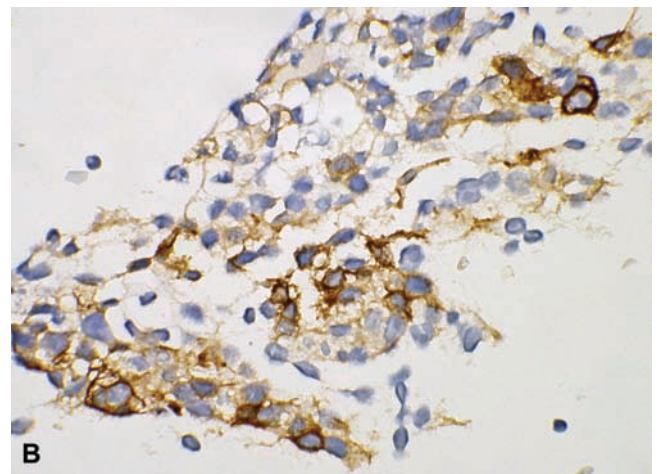
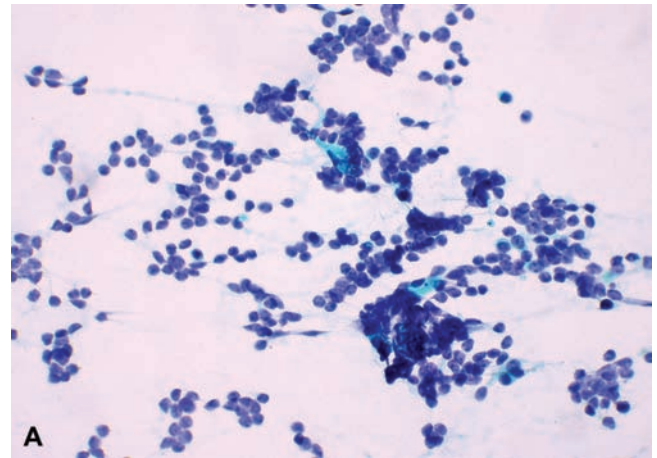


Figure 112 Olfactory neuroblastoma. (A) Smears are cellular with isolated and small clusters of round cells. Suggestions of rosette structures with central fibrillary material are seen. (B) Immunostaining for chromogranin is positive [(A) Papanicolaou stain; magnification, 200 $\times$ (B) IHC; magnification, 400 $\times$].

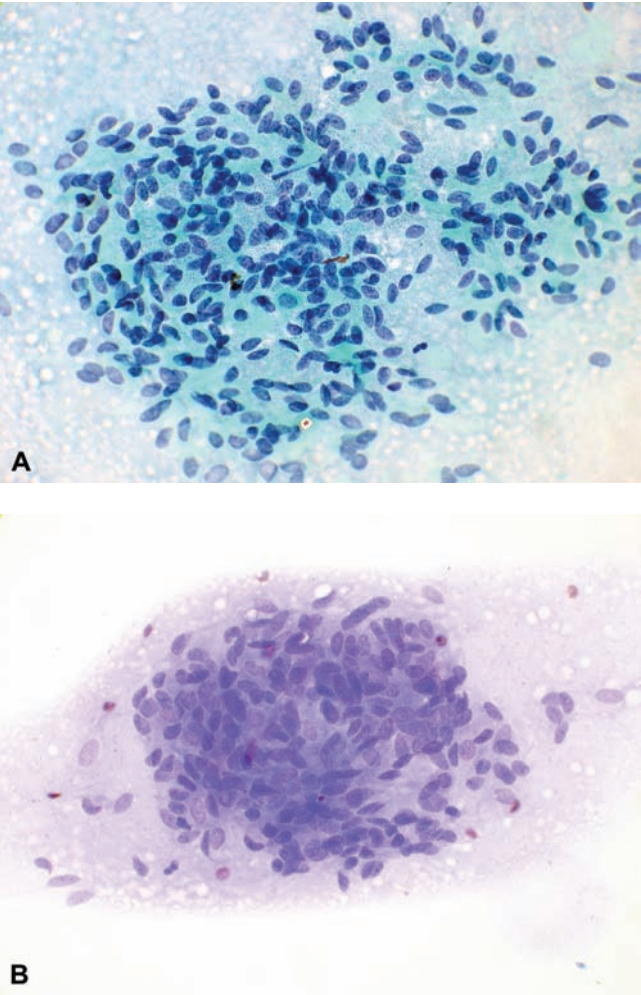


Figure 113 Olfactory neuroblastoma. FNAB shows loose clusters of cells with marked nuclear overlapping. The nuclei are uniform, round to oval, with dark, condensed chromatin. Recognition of a distinct fibrillary appearance in the cytoplasm and fibrillary material in the background are helpful in separating neuroblastoma from metastatic small cell carcinoma [(A) Papanicolaou stain; magnification, 400 $\times$ (B) DQ stain; magnification, 400 $\times$].

streaking artifact is common, but not universal, and tingible body macrophages are commonly found. Infrequently, markedly enlarged nuclei are present. Paranuclear “blue bodies” that minimally indent the tumor cell’s nuclei or are seen within the cytoplasm of tingible body macrophages are found in the majority of cases in one series (384). They are especially recognized in air-dried, cytologic material stained with DQ stain (Fig. 114).

Because of its histological similarities, primary olfactory neuroblastoma can be confused with other malignant “small” blue round cell tumors (Table 50). The presence of true rosettes and fibrillary neuropil-like background are critical in recognizing neuroblastoma (376,377). Although some studies demonstrated the presence of rosettes in more than 70% of their

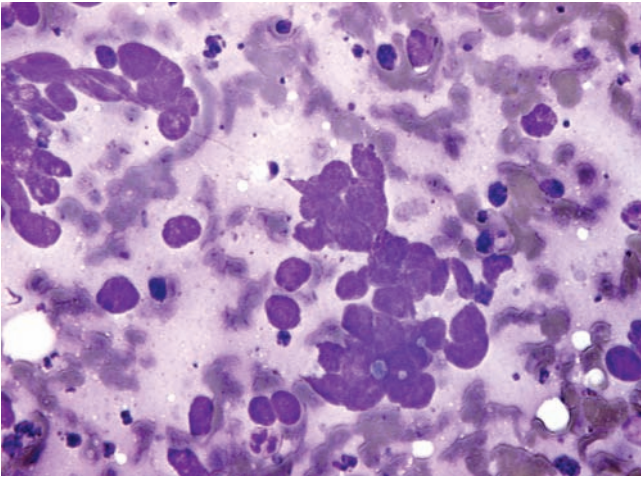


Figure 114 Olfactory neuroblastoma. Paranuclear “blue bodies” which minimally indent the tumor cell’s nuclei can be seen within the cytoplasm of the tumor cells. These blue bodies are better identified in air-dried preparation. However, they can also be seen in small cell carcinoma (DQ stain; magnification, 400 $\times$).

Table 50 Differential Diagnosis of Small Blue Round Cell Tumors of Nasal Cavity

Sinonasal undifferentiated carcinoma
Small cell neuroendocrine carcinoma (primary)
Olfactory neuroblastoma
Rhabdomyosarcoma
Melanoma
Lymphoma

cases (380), other investigators did not see any rosettes in their specimens (384). The cells of olfactory neuroblastoma can show nuclear molding, significant crushed artifact, and smudging of the nuclear material in the smears. Recognition of a distinct fibrillary appearance in the cytoplasm as well as fragments of fibrillary material in the background are helpful in separating neuroblastoma from metastatic small cell carcinoma of the lung (Fig. 113). Immunohistochemical studies may be helpful since small cell carcinoma is cytokeratins and TTF-1 positive and lymphoma is usually positive for leukocyte common antigen (LCA) and negative for epithelial markers (384).

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinoma (SNUC) can be cytologically similar to olfactory neuroblastoma. However, in contrast to olfactory neuroblastoma, SNUC cells display greater pleomorphism and may contain enlarged nucleoli (385). The tumor cells are cytokeratin, CEA, EMA positive, while synaptophysin, S-100 and chromogranin are usually negative. Paraganglioma has an immunophenotype identical to neuroblastoma (negative for keratin and positive for chromogranin, synaptophysin, and NSE, with surrounding S-100

positive sustentacular cells. However, the cytomorphology of paraganglioma is completely distinct from olfactory neuroblastoma (384).

SNUC is a rare tumor that occurs in the nasal passages and paranasal sinuses. The malignancy usually presents with nasal obstruction and septal deviation. Oral examination may reveal a large ulcerative lesion involving the maxilla, frequently extending across the midline (385,386). SNUC is highly aggressive tumor with a poor prognosis and is often inoperable.

FNA smears are highly cellular and contain poorly differentiated small- to medium-sized cells with high nuclear to cytoplasmic ratios (385–388). The cells are arranged in nests, trabeculae, and sheets. The nuclei are mildly to moderately pleomorphic. Nucleoli vary from prominent and large to inconspicuous and small (Fig. 115). Chromatin is usually homogenous and diffuse. Numerous mitotic figures, apoptotic nuclei, and necrosis are seen. Immunoreaction to cytokeratin, and EMA is identified (385,388). Chromogranin and synaptophysin are usually nega-

tive in SNUC and when positive are weak and patchy (388).

Sinonasal Neuroendocrine Carcinoma

The differential diagnosis of poorly differentiated malignant tumors of sinonasal tract includes SNUC, olfactory neuroblastoma, rhabdomyosarcoma, melanoma, and small cell neuroendocrine carcinoma (389). FNA of sinonasal neuroendocrine carcinoma are cellular and show a monotonous population of small to medium-sized cells, which can be singly dispersed, form loose aggregates and/or arranged in irregularly shaped sheets (389,390). Features of neuroendocrine differentiation can be found including rosette-like structures, and round or oval-shaped nuclei with stippled chromatin and indistinct nucleoli. There is little variation in nuclear size and shape and the cytoplasm can be poorly preserved. A fibrillary background is not seen (389,390). A high-grade neuroendocrine carcinoma with extensive necrosis, high nuclear to cytoplasm ratio, nuclear molding, pleomorphism, crush artifact, lack of nucleoli, and numerous mitoses has been described (391,392). IHC shows positive staining for chromogranin, and synaptophysin with strong diffuse cytoplasmic staining with cytokeratins (AE1/3 and CAM 5.2). Olfactory neuroblastoma usually shows abundant fibrillary material between the tumor cells, rosette-like structures and sometimes Homer-Wright or olfactory rosettes, unlike sinonasal neuroendocrine carcinoma (380,385,392). Olfactory neuroblastoma is usually negative for cytokeratin, but up to one third can show focal positivity.

Sinonasal Adenocarcinoma

Sinonasal adenocarcinoma is uncommon and may be related to exposure to wood dust and leather processing. It arises from the surface epithelium and seromucous glands. They frequently have an intestinal appearance (393). The aspirate is moderately cellular, with cohesive clusters of atypical columnar cells lying in a background of cellular debris and mucin. Individual cells are columnar and contained granular or mucin-rich cytoplasm surrounding hyperchromatic-elongated nuclei. The chromatin is coarsely granular and prominent nucleoli are frequently present (343).

Sinonasal adenocarcinoma must be distinguished from metastatic colonic adenocarcinoma. A clinical history is most helpful in this distinction. Evidence of mucin production, and glandular differentiation, separate these lesions from squamous cell carcinoma.

Paraganglioma

Carotid body tumors (paraganglioma) are benign neoplasms that arise from the autonomic nervous system. They can occur at any age but are more frequent seen in the fifth decade, manifesting as a slowly growing painless neck mass that is usually asymptomatic.

FNA cytologic findings of a carotid body tumor are characterized by low to moderate cellularity with bloody background (Table 51). Smears show

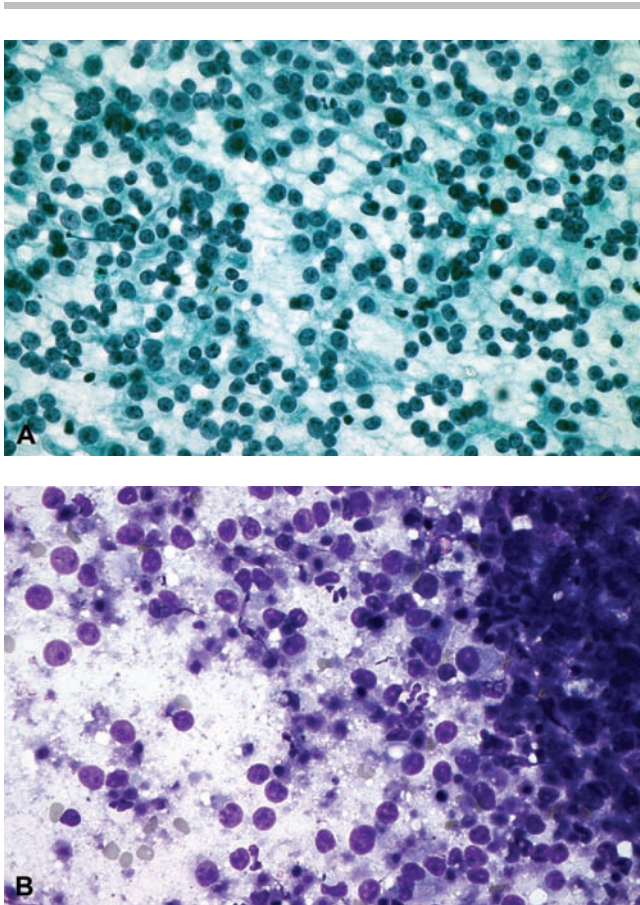


Figure 115 Sinonasal undifferentiated carcinoma. (A and B) FNAB is cellular with dyscohesive undifferentiated small- to medium-sized cells and high nuclear to cytoplasmic ratios. Nuclei are mildly pleomorphic with prominent nucleoli and frequent mitosis. Immunostaining for cytokeratin, CEA, and EMA will confirm the diagnosis [(A) Papanicolaou stain; magnification, 200× (B) DQ stain; magnification, 400×].

Table 51 Key Diagnostic Features—Carotid Body Tumor

Low-moderate cellularity with blood background
Basophilic cytoplasm with ill-defined margins
Round to spindle nuclei and prominent nucleoli
Mild to moderate pleomorphism
Fine reddish intracytoplasmic granules seen with Diff-Quik stain
Occasional intranuclear cytoplasmic inclusions

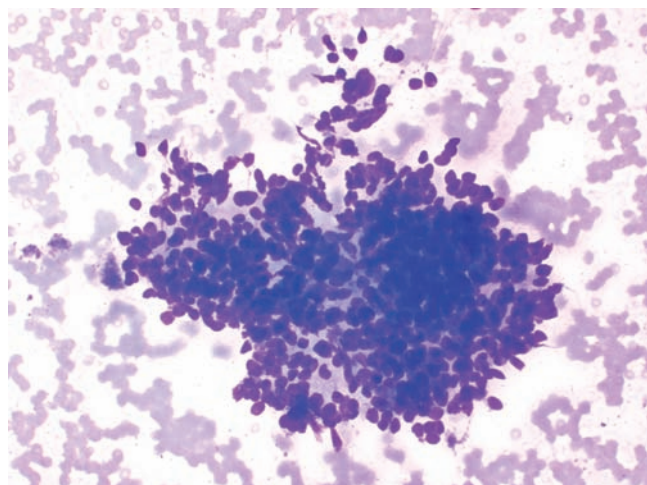


Figure 116 Carotid body tumor. Smears are characterized by moderate cellularity with bloody background. Cells are individually scattered or/arranged in clusters demonstrating an acinar/microfollicular pattern (DQ stain; magnification, 400×).

individually scattered cells or clusters, demonstrating an occasional acinar/microfollicular pattern (394–398) (Fig. 116). The cells showed moderate to abundant slightly basophilic cytoplasm with ill-defined margins and round to oval nuclei with mild to marked nuclear pleomorphism. Fine reddish intracytoplasmic granules can be seen with DQ stain. While many cells are polygonal, some can have a spindle shape. Intranuclear inclusions are occasionally present (298–401). FNA smears can show pleomorphic nuclei, prominent nucleoli, clumped chromatin with finely granular cytoplasm and occasional intranuclear cytoplasmic inclusions that can lead to a false-positive diagnosis of carcinoma (398–400) (Fig. 117). Distinguishing benign from malignant paraganglioma is difficult, but malignant lesions tend to have a tumor diathesis, mitotic figures, and more prominent nucleoli that are not seen in benign lesions.

Follicular-like arrangement and intranuclear inclusions in paraganglioma may lead to the diagnosis of PTC or a FN. Medullary carcinoma could also be in the differential diagnosis because of the presence of spindle cells and intranuclear inclusions. The anatomic location of the lateral neck mass with its prolonged history, along with a hemorrhagic FNA specimen exhibiting cytologic features of an endocrine neoplasm should help to make the correct diagnosis of paraganglioma (400,401). In challenging cases, immunohistochemical

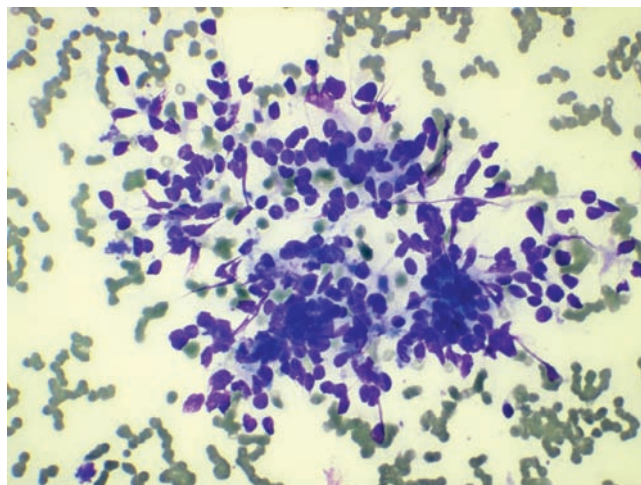


Figure 117 Carotid body tumor. The cells show moderate to abundant basophilic cytoplasm with ill-defined margins and round to oval nuclei with nuclear pleomorphism. While many cells are polygonal, some can have a spindle shape (DQ stain; magnification, 400×).

positivity for chromogranin, synaptophysin, calcitonin, and TTF-1 can confirm the diagnosis of medullary carcinoma, rather than a paraganglioma.

Heterotopic Central Nervous System Tissue (Nasal Glioma)

This congenital nonneoplastic heterotopia of neuroglial tissue usually occurs in the nasal cavity. Cytologic smears usually show hypocellularity with neural tissue containing scattered moderate-sized cells with eccentric nuclei and multiple wispy cytoplasmic processes.

VIII. THE JAW AND FACIAL BONES

A wide variety of neoplasms and cysts occur within the jaw and facial bones, including some having sufficient size to cause thinning or destruction of the overlying bone, which enables FNA biopsy.

A. Benign Fibro-osseous Lesions

Fibrous dysplasia, ossifying fibroma, and juvenile active ossifying fibroma are the currently accepted designations for these clinicopathologic processes. Aspirates of these lesions usually yield smears of low to moderate cellularity. Individual spindle-shaped cells are oval or short, with bland spindle-shaped nuclei and a fine granular chromatin pattern (402). Occasionally, three-dimensional fragments of bone or osteoid are found. These processes are cytologically indistinguishable; therefore, clinical and radiographic findings are helpful in differentiating these three entities.

B. Odontogenic Myxoma

Odontogenic myxoma is an uncommon tumor that has the potential for extensive destruction of the jaws

(403). Although, odontogenic myxoma is a benign neoplasm, it may have an infiltrative pattern, involving the facial skeleton such as the mandible or soft tissue (318).

FNA cytologic features of myxomas will reveal abundant myxoid material in which slender "spindle-shaped" or stellate mesenchymal cells are trapped (404–407). These cells have elongated nuclei with bland chromatin. The tissue fragments obtained on aspiration has a three-dimensional appearance and often have entrapped delicately branching capillaries. While the cells may appear slightly atypical, there is no evidence of nuclear anaplasia. Low cellularity and absence of cellular atypia, combined with the abundant myxoid material in the background are important features to differentiate this lesion from myxoid sarcomas (404,405).

C. Giant Cell Lesions

Giant cell lesions of the jaw and facial bones consist of four major entities represented by true giant cell tumor, giant cell reparative granuloma, aneurysmal bone cyst, and the giant cell lesions of hyperparathyroidism. All these lesions contain a mixture of small spindle-shaped to oval mononuclear stromal cells with a prominent number of multinucleated osteoclast-like giant cells (343).

Aspirates obtained from these giant cell lesions have a similar appearance, providing few clues to distinguish them (405–407). The aspirate is often highly cellular with a bloody background. The cellular component is composed of osteoclast-like giant cells and small mononucleated spindle- to oval-shaped cells (406). The nuclei of the spindle, oval and giant cells are identical in giant cell tumors, but the nuclei of the spindle-shaped cells in other lesions tend to be more elongated. Giant cells are also more numerous in the giant cell tumors, but this is often difficult to estimate on FNA. The giant cells found in true giant cell tumors have more nuclei (more than 20) than do those seen in other giant cell proliferations (343). In all these lesions, the giant cells frequently palisade around the periphery of the stromal cell clusters. Aspirates from aneurysmal bone cyst are highly bloody with a few giant cells and stromal cells scattered throughout the smears, making the diagnosis difficult. Hemosiderin is abundant in giant cell reparative granuloma, but is rarely seen in giant cell tumor (408). Open biopsy may be necessary to properly classify these lesions (408).

D. Chondroblastoma

Chondroblastoma usually presents as a lytic lesion in the epiphyseal region of long bones, but can rarely affect temporomandibular region. They tend to occur in older patients and have a high rate of local recurrence. The characteristic radiologic image is a growth-plate related, sharply defined radiolucency, containing areas of calcification with sclerotic margin. Smears are moderately to markedly cellular, composed of osteoclast-type giant cells and mononucleated round to polygonal cells occurring singly or in loose

aggregates. The mononuclear cells have dense, well-defined cytoplasm and round nuclei with thin, delicate membranes and fine chromatin. Additionally, some of the cells have reniform nuclei with nuclear grooves or folds. The majority of smears have chondroid matrix. The appreciation of the chondroblasts is the most useful feature in establishing the cytologic diagnosis (409,410).

E. Ameloblastoma

Ameloblastoma is the most common odontogenic tumor, representing 1% of all jaw lesions. This is a locally aggressive tumor, arising from odontogenic epithelial nests within the mandible (411). It usually presents as a painless swelling with nasal obstruction. Ameloblastoma is characterized by an unencapsulated growth of epithelial nests and sheets, arranged around a central zone of loosely spaced cells resembling the stellate reticulum of the enamel organ. The epithelial cells are columnar or cuboidal cells with small bland nuclei polarized away from the basement membrane (412).

FNA smears are usually cellular and contain a variable mixture of squamous, basaloid, spindle-shaped and stellate cells (413). Sheets and clusters of basaloid epithelial cells have poorly defined cytoplasmic borders, and peripheral palisading is a prominent feature (413,414). The nuclear to cytoplasmic ratios are high, with nuclei having coarse chromatin and indistinct nucleoli. The squamous cells demonstrate individual cell keratinization with a glassy hyaline dense cytoplasm and open chromatin. A few fragments of loosely aggregated spindle cells representing the stellate reticulum are often seen. The background contains granular debris, fragments of pink stroma, and inflammatory cells. Malignant cases that metastasized have demonstrated prominent cytologic pleomorphism, cellular crowding with molding and a high mitotic/karyorrhectic index (415,416).

Separation of ameloblastoma from metastatic squamous cell carcinoma may be difficult, but recognition of the basaloid cell component and prominent palisading are helpful features for the diagnosis of ameloblastoma.

F. Odontogenic Cysts and Inflammatory Cysts

Several types of cysts develop from the dental epithelium and may produce radiolucent lesions within the mandible or maxilla. FNA is rarely performed for these cysts since they are often covered by intact bone (406,407). They are subclassified on the basis of origin, histologic and radiographic findings into primordial cysts, odontogenic keratocysts, calcifying odontogenic cysts, and dentigerous cysts.

On histologic examination, all cysts show a stratified squamous epithelium lining. Cytologic examination will show small numbers of benign-appearing squamous, columnar, or cuboidal cells admixed with inflammatory cells in a watery background. An abundance of keratinizing cells and anucleate squamous

cells characterizes odontogenic keratocytes. The importance of recognizing these cysts is in establishing their benign nature and its separation from metastatic squamous cell carcinoma. In the benign cystic lesions, the squamous component will appear bland with small uniform nuclei, while squamous cell carcinomas will show significant nuclear atypia. In calcifying epithelial odontogenic tumor, sheets, and large clusters of polyhedral cells with abundant calcific material and deposits of an amorphous material are seen (417,418). Because of the lack of frank malignant cells and the presence of numerous calcific spherules and amorphous, eosinophilic material, squamous cell carcinoma and MEC can be excluded (419).

G. Intraosseous Salivary Gland Tumors

Intraosseous salivary gland tumors primarily arising in the jaw and mandible are quite uncommon. A variety of benign and malignant salivary gland neoplasms can occur, with MEC being the most frequent malignancy, which can have an aggressive course (420). The histogenesis of central intragathic salivary gland tumors has been a subject of debate with two pathogenesis proposed: (i) sialologic tissue metaplasia of odontogenic cysts or odontogenic tissue remnants, and (ii) enclaves of salivary tissue retained during embryogenesis (421).

Although most of intragathic salivary gland tumors have been diagnosed by histological methods (422–424), there are reports of FNA diagnosis of these lesions (421,424). Most intraosseous gathic mucoepidermoid carcinomas are of low grade with frequent mucinous-cell components. The presence of squamous cells, especially if atypical, associated with mucinous material is strongly suggestive of mucoepidermoid tumor (421).

IX. TUMORS OF THE EYE AND OCULAR ADNEXA

A. Introduction

Primary tumors of the orbit can arise from the adnexal glands, connective tissue (i.e., fat, vascular fibrous tissue, cartilage and bone), extraocular muscles, peripheral nervous system, and the optic nerve and its sheath. In addition, tumors of adjacent structures can invade the orbit. Lymphoid tissue is not a normal component of the orbit; however, lymphoid aggregates in the lacrimal gland become increasingly frequent with age. There are no lymphatics or lymph nodes behind the orbital septum (425).

Biopsy of the eye and its adnexa is rarely performed, even in specialized centers. The eye anatomy is complex and many cytopathologists are unfamiliar with the cytology of various ocular lesions. Early attempts with large core needle were associated with tumor extension in some cases (426,427). However, with the development of recent noninvasive imaging techniques, there is increasing confidence of ophthalmologists in obtaining samples by FNA and vitreous washing.

Orbital Cytology

The major indications for biopsy of an intraocular tumor are (i) the failure to establish a diagnosis with noninvasive imaging techniques; (ii) a confusing clinical presentation, such as an amelanotic uveal tumor with a history of a prior carcinoma; (iii) presence of media opacities, such as a dense cataract or vitreous hemorrhage with ultrasound demonstration of a choroidal mass; and (iv) patients/or oncologist unwilling to undergo definitive treatment without pathologic confirmation of the clinical impression (428–430).

Sampling Techniques

Lesions involving the skin, conjunctiva, and to the lesser extent, the cornea can be *scraped*. The lesions should be scraped gently, removing small fragments of tissue with a small spatula or blunt side of scalpel blade. Local anesthesia may be needed for conjunctival and corneal lesions (425).

The pars plana (closed) vitrectomy is the most common intraocular biopsy technique to analyze cells in the vitreous (425,427). This technique was first described by Machemer et al. in early 1970s (431,432). It has been performed as a therapeutic procedure to remove vitreous opacities due to hemorrhage and membranes and lens debris from the vitreous seen mainly in proliferative diabetic retinopathy (433).

In addition to therapeutic indications, vitrectomy is also performed for diagnostic purposes (433–437). Engels et al. (435) divided diagnostic vitrectomies into three categories: (i) Those performed to make specific diagnoses, (ii) those performed to confirm a presumed, but clinically unproven diagnosis, and (iii) those performed to diagnose a previously unsuspected condition. Vitrectomy is usually performed to rule out lymphoma, or metastatic tumors to the vitreous (436,437).

Specimens for cytologic examination can be processed using standard concentrating methods such as Millipore filtration, liquid-based procedure such as ThinPrep (Cytoc Corp., Marlborough, Massachusetts, U.S.), and AutoCyte Prep (TriPath Imaging, Burlington, North Carolina, U.S.), with results superior to direct smears. Cytospin preparations have also been successfully used (429). Occasionally, samples may contain sufficient material for a cell block (435).

We routinely perform microbiological and cytological examination of the washings collected. Immediate fixation of the specimen is preferred to prevent overgrowth of the exogenous bacteria or fungi, which can thrive in the highly nutritive vitreous fluid and, thereby, elicit a false-positive diagnosis of bacterial infection (425).

Fine Needle Aspiration Biopsy

The role of FNA in the diagnosis of intraocular tumors has been reported in a number of studies (427,438–443). Despite initial concerns that FNAB could result in tumor seeding along the needle tract (444) or produce major vision-threatening complications, it has proven to be a generally safe and reliable diagnostic technique

(445–447). FNAB has become an established diagnostic method for the evaluation of a variety of neoplastic and nonneoplastic intraocular lesions (448–452). FNA is a minimally invasive procedure without the morbidity and expense of an orbitotomy.

The diagnosis of orbital lesion is usually based on clinical and radiologic findings. However, in some occasions, the clinical and radiologic diagnoses are not conclusive, requiring a tissue diagnosis. FNAB has been used for the initial tissue diagnosis of orbital mass lesions. There are two significant advantages of orbital FNA for the primary diagnosis of lacrimal and adnexal gland lesions. First, a definitive FNA diagnosis saves the patient from unnecessary surgical intervention. Second, preoperative FNA diagnoses may help to better plan the surgical approach. FNAB is generally reserved for the following situations: (i) patients with nonresectable deep orbital lesions that require extensive surgery for diagnosis, (ii) the failure to establish a diagnosis with noninvasive imaging techniques, (iii) patients with orbital lesions who cannot tolerate a more extensive procedure, and (iv) patients unwilling to undergo definitive treatment before pathologic confirmation of the diagnosis (445,447,449,450).

Orbital examination, visual acuity, and fundus examination should be performed by the ophthalmologist. Informed consent is obtained, with an explanation of the possible complications. Patients should be informed that a negative biopsy is not definitive, and even a diagnostic FNAB does not eliminate the possibility of subsequent surgical exploration. Local anesthesia is not used because there is generally minimal pain from the FNA procedure and anesthetic injection could distort the tissue.

For orbital FNAB, we usually use 23- to 25-gauge needle, attached to a 10-mm syringe to generate negative suction. Orbital ultrasonography or computed tomography (CT) guidance, may improve the accuracy of deep orbital aspirates (453,454). The needle is introduced by the ophthalmologist through the upper or lower lid in the lateral or medial quadrants, rather than in the superior or inferior quadrants. Once the needle is in the lesion, small forward and backward movements through the lesion are made, while suction is maintained. The suction should be released prior to exit of the needle. For routine studies both alcohol fixed, Papanicolaou-stained, as well as air-dried, DQ-stained smears are prepared. Zajdela et al. described a successful series of orbital FNA without suction (455). The on-site cytopathologist may assess sample adequacy to decrease false-negative results at the time of the procedure (456). In addition, tissue culture, immunostaining, and even molecular studies can be performed on these samples (427,430,448,457).

Diagnostic Accuracy

Combining the clinical and radiologic features of orbital lesions, with the aspiration biopsy results, the diagnostic yield of orbital FNAB can be greater than 80% (458–460). In a review of 292 FNAB of palpable orbital and eyelid tumors, 87%, had a precise

histologic concordance, with less than 2% false-negative/false-positive rates and 6.3% insufficient specimens (458). However, in Krohel's series, a low cytopathologic concordance was reported with 24% nondiagnostic or insufficient specimens (461). IHC could be helpful in assessment of specimens and appropriate classification of the tumors (457). Eide et al. (443), performed IHC on over half of their patients and they were able to increase the positive predictive value of the cytologic diagnosis from 93% to 96% and increased the specificity from 67 to 83%.

There are many advantages to orbital FNAB, including high accuracy (95%) in distinguishing benign from malignant lesions and allowing an immediate diagnosis reducing patient anxiety. FNAB also obviates the need for open biopsies in 40% to 50% of cases (458). However, FNAB does not allow assessment of tissue architecture, may produce a scanty specimen and interpretation requires a trained cytopathologist. Fibrotic or desmoplastic lesions of the orbit may result in low cellular smears, with lack of diagnostic material in 10% to 18% of specimens. False-negative biopsy may occur if the needle does not enter the orbital lesion in question. Cohen et al. (462) found that tumors less than 2 mm had a higher incidence of false-negative diagnoses than those greater than 4 mm. Similarly, Augsburger et al. reported a diagnostic accuracy of 68% in small choroidal lesions (463).

Although orbital FNA is a relatively safe procedure, there are certain limitations (459). Cystic orbital lesions should not be subjected to FNAB. Patients with a bleeding diathesis, those on anticoagulation, or patients with highly vascular lesions, such as a suspected arteriovenous malformation, cavernous hemangioma, or hemangiopericytoma, should not undergo FNAB (459). Individuals with high myopia, especially those with intraocular lesions are at greater risk for globe perforation, and should be approached with care. Uncooperative patients, such as the mentally challenged or children, are poor candidates for orbital FNAB (459).

The risk of needle tract recurrence with the use of FNA (21–25 gauge) biopsy is exceedingly low. Henderson suggested that solid masses of lacrimal gland should not undergo FNA because of the risk of disseminated disease (464). However, no case of tumor seeding due to the aspiration has been reported. In cases of suspected retinoblastoma, aspiration is contraindicated because of the risk of spread along the needle track of this notoriously “sticky” tumor (465). Some authors have reported experimental data, suggesting that there is a risk of needle tract seeding of melanoma cells (447,466). Shields et al. have recommended enucleation within 24 hours of biopsy of a proven malignant neoplasm (466).

Complications of orbital FNA are not common, but can be serious. The more common complications are retrobulbar hemorrhage and retinal detachment. The most serious uncommon complication is eye perforation, which may require cryoretinopexy (467,468). Retrobulbar hemorrhage following FNAB usually resolves without ocular sequelae. Other complications of FNAB include transient visual loss,

ocular motility disturbance, and ptosis (468). Lesions directly over the vertical aspects of the globe are associated with a greater risk of scleral perforation.

B. Benign Lesions

Infections

Viral diseases. Viral diseases include molluscum contagiosum, verruca vulgaris, herpes zoster, and herpes types 1 and 2, which can infect the lids and conjunctiva. Some of these diseases are frequently sexually transmitted and can be sight threatening. Viral disease is not usually diagnosed by cytology alone, but it is possible to diagnose poxvirus induced molluscum contagiosum by identifying eosinophilic, rounded cytoplasmic inclusions. Similarly, virus induced verruca vulgaris and the effects of the herpes simplex viruses 1 and 2 can be diagnosed by cytological techniques (425,428). Cytomegalovirus (CMV) infection can also be seen in immunocompromised patients (469). Corneal scrapings showed many enlarged cells with characteristic CMV nuclear inclusions. The diagnosis can be confirmed by in situ hybridization, and viral culture.

Bacterial and fungal conjunctivitis. Bacterial and fungal conjunctivitis are best diagnosed by culture (470,471). Cytology may be helpful in detecting unusual infections such as actinomycosis, acanthamoebic keratitis (472), or blastomycosis, especially when the organisms are superficial. In HIV and immunosuppressed patients, intraocular infections are more common. FNA has been used to diagnose intraocular aspergillosis, mucormycosis (Fig. 118) and coccidioidomycosis (473,474). Cytologic examination of aqueous humor can reveal inflammatory cells (i.e., polymorphonuclear leukocytes, histiocytes-macrophages, and lymphocytes), cocci or other microorganisms (475,476). The collected sample in the syringe should be immediately sent to the laboratory: half mixed with an equal amount of 50% ethanol solution and fresh specimens for microbiologic examination.

Vernal conjunctivitis. Vernal conjunctivitis is a recurrent hypersensitivity reaction of the conjunctiva, occurring in atypical allergic patients. Patients have increased levels of IgE in the serum and tears (477). This condition may mimic other causes of "red eye" and may be subjected to microscopic evaluation. The resulting smears contain inflammatory cells, including eosinophils, mast cells, basophils, and lymphocytes. If the condition is chronic, goblet cells may be abundant. Careful search for signs of *Chlamydia* is important, because the treatment of the two diseases is different.

Chlamydial conjunctivitis (trachoma). Chlamydial conjunctivitis (trachoma) has characteristic inclusions, which can be appreciated in conjunctival smears in 8% of patients (478,479). Naib correlated perinatal ocular and maternal genital infections concluding that 61% of 54 mothers of a set of infected newborns had diagnosable *Chlamydia* in recent cervical smears (480). PCR shows comparable results to standard McCoy cell culture, with equal specificity and more sensitivity (479).

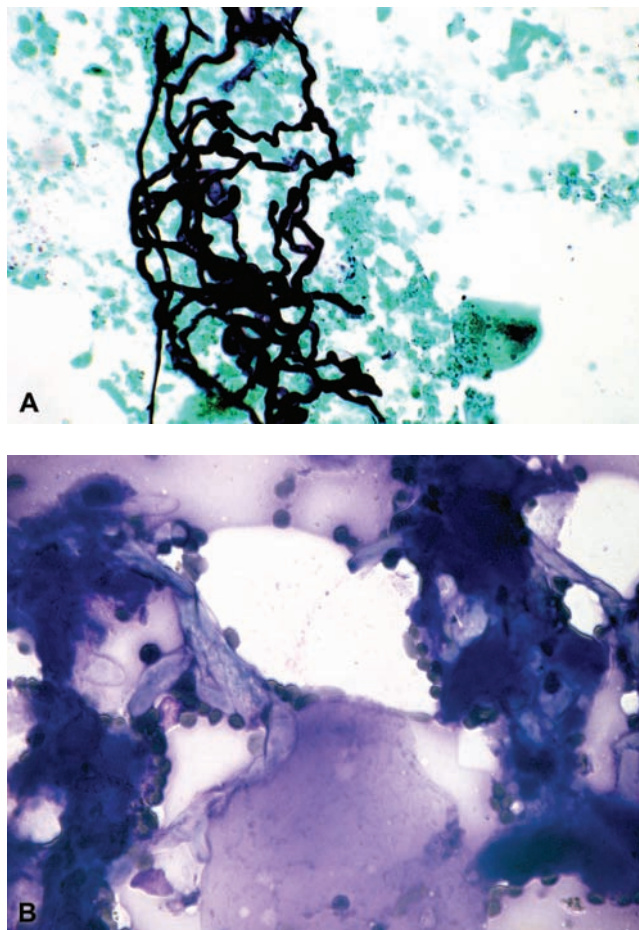


Figure 118 Orbital fungal infection: FNA technique can be used to diagnose orbital fungal infection. Smears usually show necrotic background with mixed chronic inflammatory cells. (A) Aspergillus species with abtuse branching septate hyphae, better seen with special fungal stain. (B) Mucormycosis infection in diabetic patient demonstrates ribbon-like, pale-staining, pauciseptate, branching hyphae [(A) Silver fungal stain; magnification, 200× (B) DQ stain; magnification, 600×].

A number of entities can mimic ocular infection including ghost cell glaucoma, phacolytic glaucoma, phacoanaphylactic endophthalmitis, and iridocyclitis (475). In general, a more dense infiltration by neurophils and lymphocytes supports the diagnosis of infectious endophthalmitis, even in the absence of micro-organisms in the cytologic specimens of the aqueous humor.

Ghost cell glaucoma. In ghost cell glaucoma, RBCs are present in the vitreous for an extended period losing their hemoglobin. They become ghost erythrocytes leading to mechanical obstruction and glaucoma. The cytological findings are pathognomonic, when numerous ghost erythrocytes in the absence of inflammatory cells are identified.

Phacolytic glaucoma. Phacolytic glaucoma may occur exogenously after lens damage by traumatic disruption or endogenously with hypermature cataract.

Phacolytic cells are swollen histiocytes with lightly eosinophilic granular cytoplasm and lens material. These cells can be seen in anterior chamber aspirate specimens causing mechanical obstruction of the anterior chamber angle (481). Cytologically, the presence of lens material and phacolytic large macrophages with the synchronous absence of an inflammatory reaction are characteristic.

Phacoanaphylactic endophthalmitis. Phacoanaphylactic endophthalmitis develop infrequently after hypermature cataracts, or cataract surgery (481,482). The cytologic findings may demonstrate granulomatous or a nongranulomatous inflammation (481). The negative microbiological culture and the clinical outcome (response to the removal of the lens or lens remnants and corticosteroids) support the diagnosis.

Idiopathic orbital inflammation (Sclerosing Orbititis). Also referred to as inflammatory pseudotumor, idiopathic orbital inflammation (sclerosing orbititis) in the acute form has an abrupt onset of pain, injection, chemosis, and decreased ocular motility. The inflammation involves orbital soft tissues including fat, extraocular muscle, tendon, lacrimal gland, and blood vessels (483,484). In the chronic form, there is marked fibrosis that may envelop the structures of the orbit and mimic a malignant neoplasm. Occasionally FNAB may be performed and revealed scant aspirates with a few fibroblasts and lymphocytes.

Granulomatous Lesions

Foreign body granuloma. Foreign body granuloma may present with a subconjunctival or orbital lesion. Usually patients are not aware of a previous injury or implanted foreign material. Patients present with a red eye and reduced eye movements. FNA demonstrates granulomas with foreign-body type giant cells. Infections should be excluded with culture and special stains (Table 52).

Chalazions. Chalazions are lipogranulomatous reactions of the eyelid, occurring when Meibomian gland obstruction occurs secondary to inspissated secretions (485). These painful swellings are caused by retained secretions of the Meibomian glands and are characterized by a mixture of lipogranulomatous and suppurative inflammation. Occasionally the chalazion may present as a discrete nodular mass, mimicking a sebaceous carcinoma (447,485). Smears of the aspirate show numerous histiocytes with foamy cytoplasm and occasional granulation tissue.

Dermoid cyst. Dermoid cyst is the most common orbital tumor in children. It is preferable not to aspirate a dermoid cyst to avoid spillage of its contents (485).

Table 52 Differential Diagnosis of Orbital Granulomatous Lesions

Chalazions
Dermoid cyst, ruptured
Infections
Wegener's granulomatosis
Sarcoidosis
Whipple disease

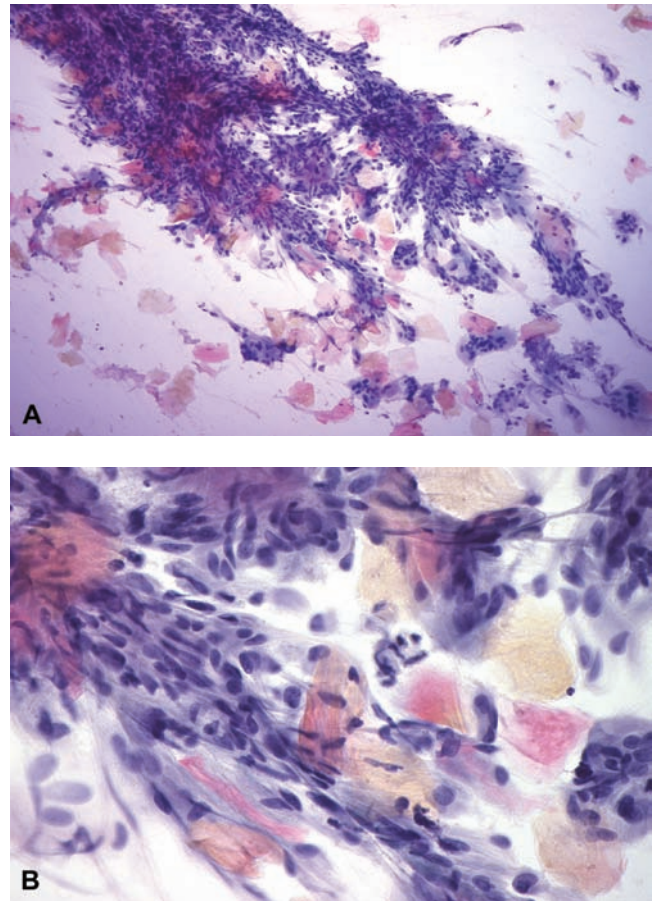


Figure 119 Ruptured dermoid cyst. Smears show anucleate squamous cells, keratin debris, and granulomatous inflammation with multinucleated giant cells [Papanicolaou stain; (A) magnification, 200× (B) magnification, 400×].

However, deep dermoids and those with extension through bone sutures are frequently difficult to diagnose clinically and may be subjected to FNA (458). FNA contains anucleate squamous cells, keratin debris, and occasionally hair shafts. A ruptured dermoid cyst will also contain granulomatous inflammation with multinucleated giant cells (Fig. 119).

Wegener's granulomatosis. Wegener's granulomatosis is characterized by necrotizing vasculitis and granulomatous inflammation in the upper respiratory tract, lung, and kidneys. Orbital involvement occurs in about 20% of the cases and is usually bilateral. These lesions frequently have extensive fibrosis with scanty, non-diagnostic FNA specimen.

Sarcoidosis. Sarcoidosis occurs more frequently in black women, involving lacrimal glands in 7% of patients. Ocular sarcoidosis can clinically simulate a neoplasm. FNA demonstrates granulomatous inflammation without necrosis (Fig. 120). Multinucleated giant cells are usually evident. Culture and special stains are needed to rule out an infectious etiology.

Whipple disease. Selsky et al. (486) reported ocular involvement in a patient with Whipple's disease.

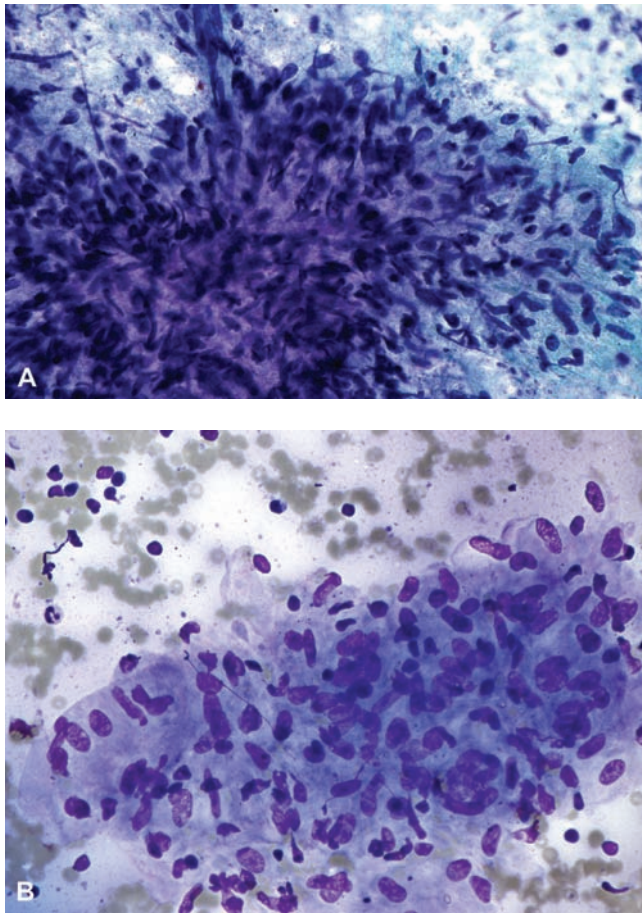


Figure 120 Granulomatous inflammation. (A) Granulomatous reaction with chronic inflammation and extensive necrosis usually results from infectious agents. (B) Sarcoidosis aspirates demonstrate granulomatous inflammation with clean background and occasional multinucleated giant cells. Sarcoidosis is the diagnosis of exclusion after negative special fungal stains with clinical and serological correlation. [(A). Papanicolaou stain; magnification, 400× (B) DQ stain; magnification, 400×].

Characteristic vitreous opacities and retinitis, with consequent compromised visual acuity, are a result of infiltration of the tissue with foamy macrophages. These benign histiocytes contain intracytoplasmic PAS positive material. Electron microscopy discloses bacillary bodies. Many patients respond favorably to antibiotics.

C. Benign Neoplasms

Ectopic lacrimal glands may be aspirated and are composed of clusters of acinar cells, having small bland nuclei. These glandular groups should not be confused with adenocarcinomas, in which the nuclei have malignant features.

Cavernous Hemangiomas

Cavernous hemangiomas are well-encapsulated tumors located behind the eyeball within the boundaries

of the rectus muscles and composed of large vascular channels. The vessel walls contain smooth muscle and there is fibrous tissue in the trabeculae that separates the vessels. Radiologic studies show a rounded mass with smooth contours. Although it would be preferable to not aspirate this lesion because of the risk of orbital hemorrhage, FNA of few cases have been performed without complications. FNA specimen reveals only bloody smears (447,459).

Hemangiopericytoma

Hemangiopericytoma is a vascularized tumor with characteristic staghorn appearance of vessels, and interspersed spindle cells. The clinical findings include proptosis, palpable mass, pain, and diplopia. FNA reveals spindle and oval cells with occasional branched vessels.

Mucocoeles

Mucocoeles are tumors composed of extracellular mucous debris, caused by obstruction of the ostia of the sinuses. The frontal sinus is the most common origin for orbital mucocoeles (487). FNA reveals a large amount of mucoid material with occasional vacuolated macrophages (mucophages).

Pilomatrixoma

Pilomatrixoma is a benign neoplasm that appears as subepidermal nodule in the head and neck region, most commonly in children and young adults. Cytologically, pilomatrixomas are characterized by cellular smears with three cell populations (488,489) (Fig. 121). The first is of the small basaloid type, with scanty cytoplasm and round regular nuclei. The nuclear chromatin of these cells is finely granular and evenly distributed. The second is of the squamous cells type, with bland nuclei and evidence of keratinization. The third, which is the epithelial cell type, is the shadow or ghost cell, showing a high degree of keratinization and lacks demonstrable nuclei. The ghost cells are most easily seen on air-dried material, but are also recognized on Papanicolaou-stained smears. They frequently have a pale, poorly discernible cytoplasm and often appear only as outlines of cells. In addition to the epithelial component, scattered multinucleated foreign body giant cell reaction to the keratinous material is often present. A pitfall for a false-positive diagnosis is not recognizing the presence of ghost cells and misinterpreting the basaloid cells as a high-grade malignancy (489).

Pleomorphic Adenoma

Pleomorphic adenoma of the lacrimal gland usually presents as slow growing, painless mass, accounting for 50% of epithelial lacrimal gland tumors (490–492). It has been suggested that open biopsy of lacrimal pleomorphic adenoma may lead to needle-tract seeding (464). However, no documented case of seeding following FNA has been reported. Smears show

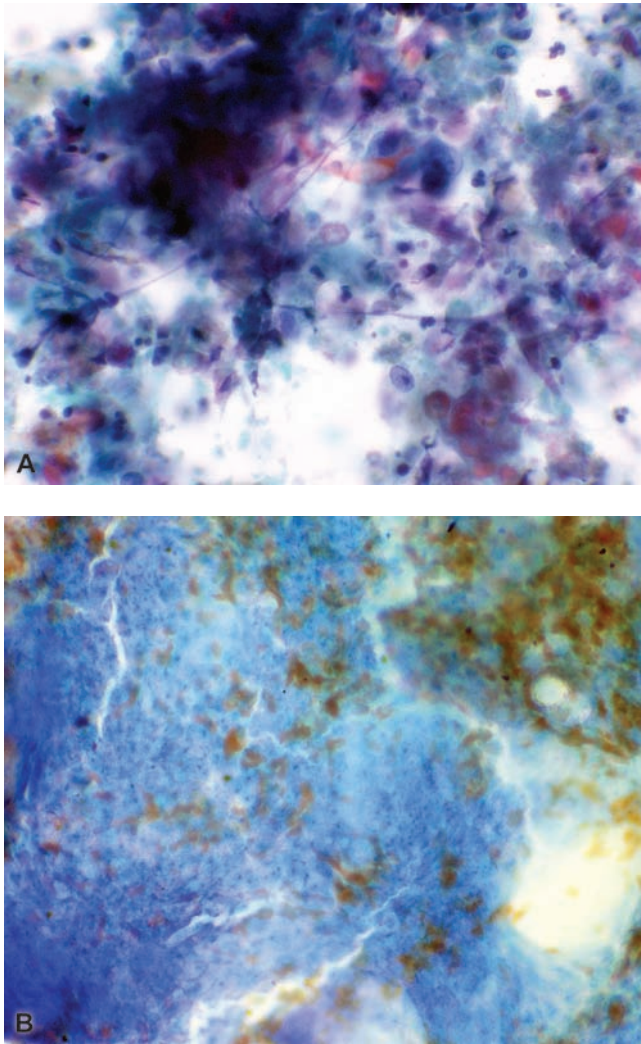


Figure 121 Pilomatrixoma. Smears are cellular with distinctive two cell populations. (A) Small basaloid cells with high nuclear to cytoplasmic ratio, high mitotic activity, and apoptosis. (B) Clusters of benign anucleated squamous (shadow or ghost) cells. The ghost cells are most easily seen on air-dried material [(A and B) DQ stain; magnification, 400 $\times$].

similar cytologic features of pleomorphic adenomas seen in the major salivary glands.

Meningioma

Although meningioma can involve the orbit by extension from the intracranial space, the lesion may also arise from the meninges covering the optic nerve and present as a retrobulbar mass within the orbit. Meningiomas may compress the optic nerve and lead to hearing and visual deficits (493,494). The optic nerve may show fusiform swelling, diffuse thickening, or globular enlargement (485). FNA can effectively diagnose orbital meningiomas. The aspirate is composed of small ovoid nuclei with scant cytoplasm (446,447, 494–496). Nuclei demonstrated fine chromatin,

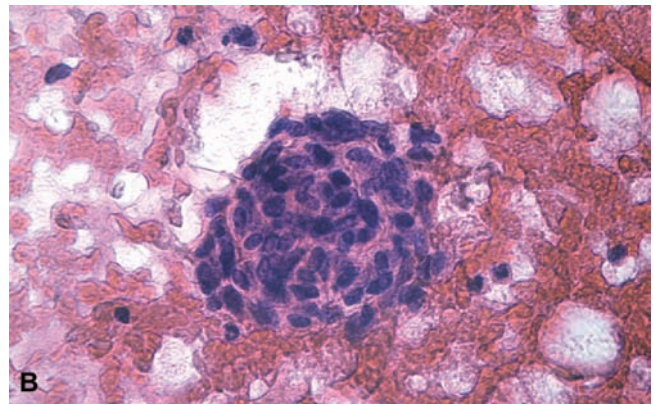
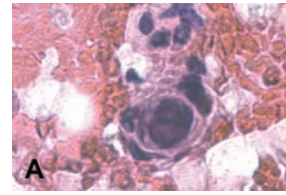


Figure 122 Orbital meningioma. Smears show bland round-oval cells with smooth nuclear membranes and fine chromatin. The meningothelial cells tend to aggregate in whorls arrangement. (Inset) Psammoma bodies can be occasionally seen (Papanicolaou stain; magnification, 400 $\times$ (Inset) magnification, 600 $\times$).

inconspicuous nucleoli, and occasional nuclear pseudoinclusions. The classic three-dimensional concentric whorls of these cells (noncalcified psammoma bodies) provide for the conclusive diagnosis (496) (Fig. 122). Psammoma bodies are not present as frequently in primary central nervous system (CNS) meningiomas. Reactive meningeal hyperplasia can be seen with optic nerve gliomas and metastatic carcinomatous meningitis.

Schwannoma (Neurilemmoma)

Schwannoma (neurilemmoma) occurs in patients aged between 20 and 50 years and can be separated or associated with neurofibromatosis. Clinically, patients frequently exhibit proptosis, lid swelling, diplopia, and indentation of the posterior sclera (485). FNA of schwannoma is usually not diagnostic because scant material is obtained as a result of the cohesive architecture of the neoplasm (459). However, when a myxoid background is associated with spindle cells and wavy nuclei are seen in the smears, the possibility of neural lesion can be suggested. Positivity for S-100 will support the neural origin of these tumors.

D. Malignant Tumors

Basal Cell Carcinomas

Basal cell carcinomas are the commonest malignant lesion of the eyelid and the cytodiagnostic method of

choice is scraping the lesion. Basal cell carcinomas usually occur in elderly patients who have had a long exposure to sunlight and are commoner in the lower lids. They are usually single lesions, but can be multiple in patients with xeroderma pigmentosum. Because of their proximity to the eye, exenteration of the orbit and loss of the globe may be necessary to control the disease in neglected cases. These lesions are often easily recognized clinically and are readily amenable to undergo shave or excisional biopsy. However, occasionally, recurrent basal cell carcinomas will undergo FNA (425).

The material produced by scraping appears white or translucent and spreads easily on the slide and/or separates into small fragments. This appearance is characteristic for basal cell carcinoma. Smears demonstrate clusters of small dark basaloid cells with scant cytoplasm, and distinct cell border. Cytologic examination reveals nuclear palisading along the edges of the cell clusters (497). The individual cells show monomorphic nuclei with finely granular hyperchromatic chromatin and occasional nucleoli. Mitoses are rare except in rapidly growing tumors. In cases with marked pleomorphism, squamous carcinoma should be excluded.

Squamous Cell Carcinoma

Squamous cell carcinoma of the eyelid is less common than basal cell carcinomas. Squamous carcinomas can also occur at the limbus and conjunctiva, in contrast to basal cell carcinoma. Squamous cell carcinoma is also the most common paranasal sinus tumor to invade the orbit (498). The clinical appearance is that of an indurated ulcer with a raised irregular border. Scraping is frequently painless, although the lesions usually easily bleed. Patients with squamous carcinoma of a sinus involving the orbit have a poor prognosis (498).

Scraping usually produces numerous single cells due to the lack of cellular cohesion. The cytologic appearances vary according to the degree of differentiation. Poorly differentiated squamous cell carcinoma has cells with large vesicular nuclei, prominent nucleoli, pleomorphism and lack of polarity, and most importantly, the presence of intercellular bridges. In well-differentiated squamous carcinoma, the diagnosis is readily made, especially in the Papanicolaou-stained smears. Typically, some of the cells may be highly keratinized with dense organeophilic cytoplasm. Nuclei with malignant features are present, but there are often degenerative forms having dark hyperchromatic and/or opaque pyknotic nuclei. Anucleate necrotic "ghost" cells are almost always present (493). Smears often contain large numbers of neutrophils in the background and a granulomatous reaction can be present as a reaction to the keratinizing debris (Fig. 123). A pitfall for a false-positive diagnosis of malignancy is a scraping from benign skin ulcers, where the smears from the healing edges may contain reparative atypical squamous cells, and occasional mitotic figures. However, these benign ulcers are nearly always painful and difficult to scrape unlike squamous carcinoma.

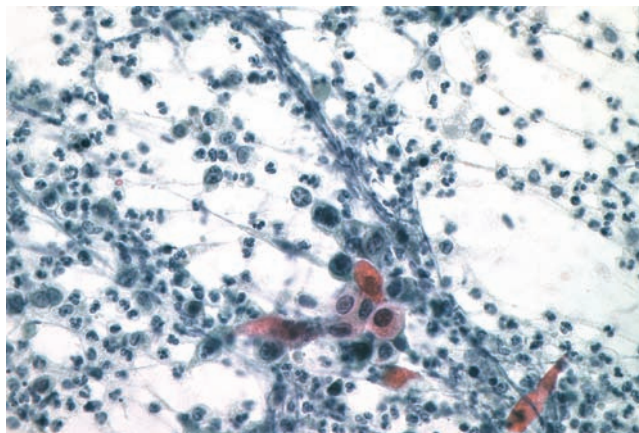


Figure 123 Kertinizing squamous cell carcinoma. FNAB may show large numbers of neutrophils in the background, leading to false-negative diagnosis. Looking for the atypical keratinizing cells may give a clue for the appropriate diagnosis (Papanicolaou stain; magnification, 400 $\times$).

Adenoid Cystic Carcinoma (ACC)

ACC accounts for about 25% to 30% of all epithelial lacrimal gland tumors (490,499). In addition, ACC can be metastatic from lung (500). Clinically, the patients usually have symptoms of pain and develop a mass in the lacrimal fossa. With CT scan, ACCs are globular tumors, but frequently have irregular destructive margins around orbital bone (501). FNA cytologic features have been previously discussed in this chapter.

Sebaceous Carcinoma

Sebaceous carcinoma of the eye is a rare tumor, representing 5% of malignant epithelial tumors and frequently involves the lower eyelid (502). Sebaceous carcinoma arises from either the Meibomian glands or the glands of Zeiss. The clinical diagnosis of sebaceous carcinoma is difficult since it can simulate other eyelid lesions (503,504). Sebaceous carcinoma may present as a small yellow nodule (mimicking chalazion), a diffuse thickening of the eyelid (mimicking blepharitis), or a mass in lacrimal fossa (504). Sebaceous carcinoma are aggressive tumors, especially when they arise around the ocular adnexae, requiring wide excision and careful follow-up is needed to detect metastases (504).

FNA of sebaceous carcinoma has been reported in case reports and series of eyelid tumors (487,505–507). Aspirate smears are usually cellular consisting of large cell aggregates and individually scattered cells (487,507). Many of the cells within the aggregates are necrotic or degenerated, with densely clumped, fragmented chromatin. The smear background generally contains abundant necrotic debris and fragments of degenerating cells. Individual cells have moderate to abundant cytoplasm, which frequently has a foamy, or finely reticular or bubbly, sebaceous appearance. The nuclei are enlarged with coarse chromatin and

prominent nucleoli. Generally, mitotic figures are easily identified. Oil red O stains will demonstrate intracellular fat. A second population of basaloid cells with small dark nuclei and scant cytoplasm is seen in the smears. Multiple biopsies to determine the extent of the tumor is recommended, since sebaceous carcinoma in the eyelid can be multifocal in up to 10% of cases (485).

Merkel Cell Tumor

Merkel cell tumor is a primary carcinoma of the skin with neuroendocrine features, occurring most frequently in elderly individuals. The face and upper extremities are common sites of origin. Aspirates from Merkel cell tumor are cellular, with the majority of cells individually scattered with occasional rosette-like clusters or three-dimensional groups (508–510) (Fig. 124, Table 53). Nuclei are enlarged, with a finely granular evenly dispersed chromatin pattern. The nuclear membranes are delicate, and nuclear molding is generally absent, a feature helpful in distinguishing Merkel cell tumor from metastatic small cell carcinoma of the lung (Fig. 125). The nuclear distribution is uniform and fine imparting a “salt,” rather than the coarse and fine “salt and pepper” chromatin of small cell carcinoma. Mitotic figures are plentiful. A feature of diagnostic aid is the presence of perinuclear deposits best seen on Papanicolaou staining (508). IHC

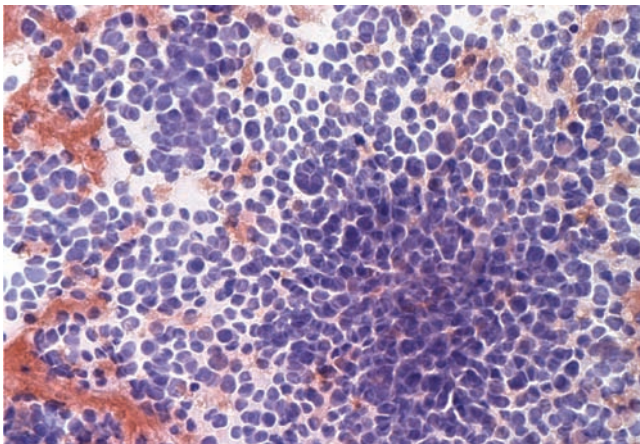


Figure 124 Merkel cell carcinoma. Smears are cellular with small round blue dyscohesive malignant cells. The cells demonstrate large nuclei and a finely granular evenly dispersed chromatin. The nuclear membranes are delicate, and nuclear molding is generally absent (Papanicolaou stain; magnification, 400×).

Table 53 Key Diagnostic Features—Merkel Cell Carcinoma

Cellular smears with individually scattered cells
Large nuclei with finely granular, evenly distributed chromatin
Delicate nuclear membranes
Nuclear molding is usually absent (in contrast to small cell carcinoma)
Tumor cells are positive for CK20 and negative for CK7 and TTF-1

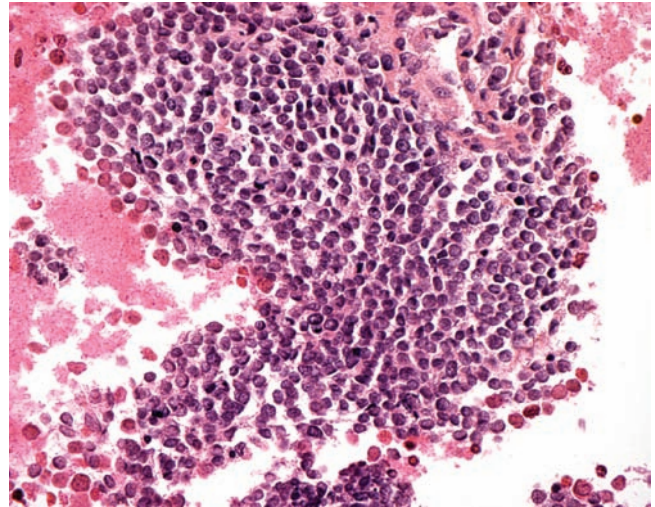


Figure 125 Merkel cell carcinoma. Formalin-fixed, paraffin-embedded cell block section shows the characteristic nuclear features of Merkel cell carcinoma, imparting a “salt,” rather than the coarse and fine “salt and pepper” chromatin of small cell carcinoma. Immunostaining for CK20 and negative staining for TTF-1 and CK7 support the diagnosis of Merkel cell carcinoma and exclude metastatic small cell carcinoma (H&E stain; magnification, 400×).

staining demonstrates the presence of neuron specific enolase (NSE), neurofilament, and a characteristic pattern of CK-20 perinuclear, dot-like positivity, and negativity for TTF-1 and CK7.

Orbital Teratomas

Orbital teratomas are rare, but they form an important differential diagnosis in neonatal orbital masses. Only a few FNA cases of orbital teratomas with malignant changes have been reported (511–513). The eye may show proptosis, lid edema, conjunctival chemosis, and a keratinized cornea. Orbital teratoma is usually multiloculated, cystic masses with solid areas, compared with the unilocular cystic lesions such as dermoid and epidermoid inclusion cysts (513). Malignant teratomas are of three types: teratomas with germ cell tumors, teratomas with nongerminant malignant tumors (carcinoma and sarcoma), and immature teratomas that metastasize. FNA cytologic features are dependent on the components sampled and the type of teratoma (513).

Retinoblastoma

Retinoblastoma is the most common intraocular neoplasm occurring in infants and children (514). It is derived histogenetically from primitive neuroepithelial cells that have the potential to differentiate into the three layers of sensory retina, i.e., neurons, astrocytes, and photoreceptors (rods and cones) (515). Histologically, the tumor is characterized by the presence of undifferentiated small round cells with a variable tendency to form Flexner-Wintersteiner rosettes.

Table 54 Key Diagnostic Features—Retinal Neuroblastoma

Cellular smears with necrotic debris and inflammatory background
Two types of dyscohesive cells: undifferentiated cells (small round cells) and cells with early photoreceptor differentiation (abundant, pale staining cytoplasm with cytoplasmic process)
Flexner-Wintersteiner rosettes formed by peripheral arrangement of nuclei with fine central fibrillary cytoplasmic process.
However, a significant number of cases may not show this feature.

Cytological smears are hypercellular with single cells and cohesive clusters in which nuclear molding can be present (515–519) (Table 54). Smears show necrotic debris and inflammatory cell in the background. The single cells can be divided into two types with several transitional forms. The first cell type includes undifferentiated cells with high nuclear to cytoplasmic ratios, and markedly basophilic cytoplasm (449,520). These cells are indistinguishable from the undifferentiated cells present in other small round-cell malignant tumors of childhood (515) (Fig. 126). The second cell type shows abundant, pale staining cytoplasm with peculiar cytoplasmic processes. These processes are usually short and “hump-like,” although occasionally they can be long and slender. The presence of these cytoplasmic processes is probably an indication of early photoreceptor differentiation. The nuclei usually reveal deep indentations (451).

Flexner-Wintersteiner rosettes are formed by peripheral arrangement of nuclei with fine central fibrillary cytoplasmic processes. Florets with photoreceptor cell differentiation are found only in

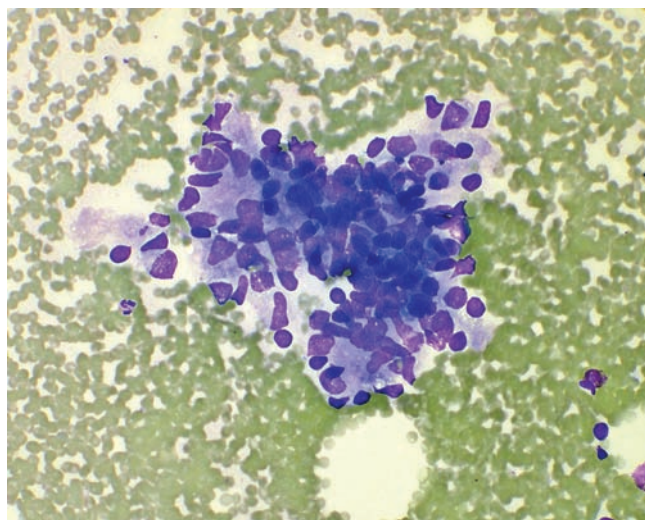


Figure 126 Retinal neuroblastoma. Smears are cellular with Flexner-Wintersteiner rosettes, formed by peripheral arrangement of nuclei with fine central fibrillary cytoplasmic processes. The cells are elongated with early photoreceptor differentiation (DQ stain; magnification, 400 $\times$).

well-differentiated retinoblastomas (Fig. 126). The presence of Flexner-Wintersteiner rosettes is considered to be an important morphologic feature for the diagnosis of retinoblastoma (449,515,520); although, in a significant number of cases, they may not be seen (521,522).

As many as 16% of eyes removed with the clinical diagnosis of retinoblastoma contain a simulating lesion (517). The main differential diagnoses are vitreous hemorrhage, Coat's disease, and ocular toxocariasis (517). Coat's disease is suspected cytologically when a subretinal aspirate reveals foamy macrophages, which frequently contain coarse, oval melanin pigment. Inflammatory cells (especially lymphocytes) are also noted (450). In toxocariasis, cytological aspiration reveals a predominance of eosinophils. In vitreous hemorrhage, the FNA consists erythrocytes without any tumor cells (450). Metastatic neuroblastoma can occur within the eye including the orbit, which may lead to diagnostic confusion with retinoblastomas (518). Flexner-Wintersteiner rosettes are more usually associated with retinoblastoma than neuroblastoma. History is crucial in this differential diagnosis.

The diagnosis of the great majority of retinoblastoma can be achieved with noninvasive techniques, including indirect ophthalmoscopy, ultrasonography, and imaging procedure (CT and MRI). Shields and Shields (517) reported only 2 FNA out of 500 referred patients with a questionable retinoblastoma diagnosis. The utilization of FNAB for the diagnosis of retinoblastoma is controversial among ophthalmologists and ocular oncologists. Some authors have reported the usefulness of this procedure in cases with diagnostic clinical uncertainty (449). Other investigators have argued against FNAB because of the possibility of tumor seeding and spread outside the globe (518,519). There is no question that tumor seeding of the needle tract takes place, but the long-term viability of the spilled tumor cells causing extraocular spread is questionable (518). Tumor growth outside of the globe is a rare but a serious occurrence. Therefore, FNAB should be limited to the extraordinarily unusual clinical circumstance such as parents requesting histopathologic verification of retinoblastoma before definitive treatment, (especially enucleation), and recurrent or metastasis of retinoblastoma in extraocular tissues (516,518,519,523).

Metastatic Carcinoma

The frequency of ocular metastases has been reported to be about 1% from grossly detectable orbital lesions and 12.6% for microscopic metastases (425,524). Most metastatic cancers occur in the uveal tract, while metastases to the retina and optic disc are rare (524–526).

Although metastases to the orbit usually reflect disseminated disease, the occurrence of a metastatic deposit in this region may rarely be the initial presentation of a patient's malignancy (527). When metastases do occur in the region of the eye, they are commonly from the breast in women, from the lung in men, and

from neuroblastomas in children (527,528). Small cell carcinoma is the most common type of lung cancer that metastasizes to the orbit. It is important to recognize the possibility of metastases since the orbital findings are sometimes the initial manifestations of the malignancy. The cytologic findings of small cell carcinoma can mimic another small cell neoplasms such as lymphoma. The differentiating cytologic features include diffuse salt and pepper chromatin, lack of prominent nucleoli, nuclear molding, cell necrosis (apoptosis), and nuclear crush artifact.

A variety of orbital metastases from other different organs have been reported such as mucinous ovarian carcinoma (528,529), ovarian carcinoma (530), chordoma (531) (Fig. 127), ACC from salivary glands and bronchial epithelium (532,533), hepatocellular carcinoma (534,535), and carcinoids (536). Contrary to the pattern of eye metastases in general, metastases from the thyroid gland tend to involve the orbit more commonly than the globe (537,538). Orbital invasion by tumors from adjacent structures is also common.

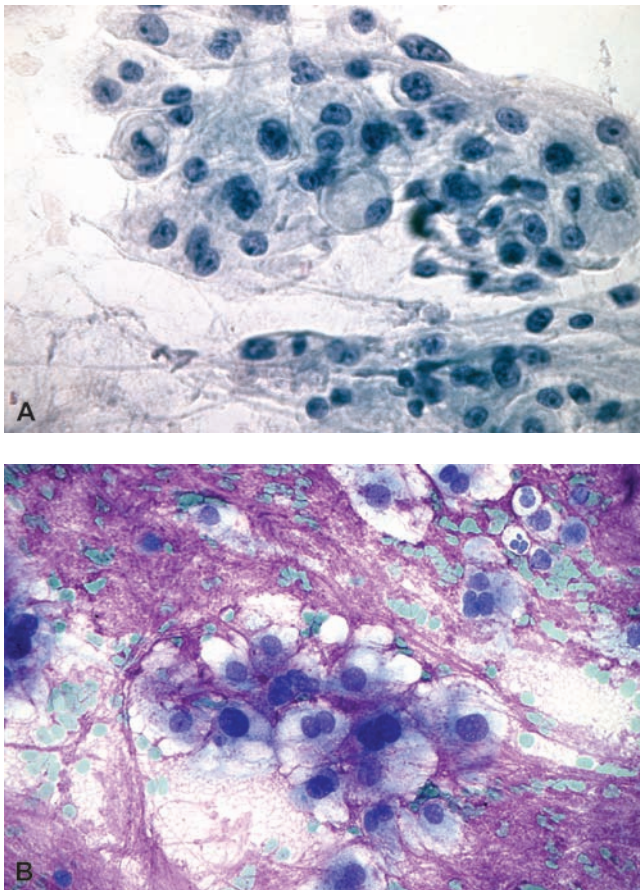


Figure 127 Metastatic chordoma to the orbit. (A) FNAB shows tumor cells with low nuclear to cytoplasmic ratio, bubbly vacuolated cytoplasm, and relative bland nuclei (physaliferous cells). (B) Chondromyxoid metachromatic stroma is wrapping around physaliferous cells, better seen in DQ [(A) Papanicolaou stain; magnification, 400× (B) DQ stain; magnification, 400×].

E. Melanocytic Lesions

Melanotic Neuroectodermal Tumor of Infancy

Melanotic neuroectodermal tumor of infancy is a rare, usually benign neoplasm, involving the anterior alveolar ridge of the maxilla (539), but it has also been described in other sites. CT and MRI are used to determine the amount of bony invasion and involvement of important structures (540,541). Increased levels of vanillyl-mandelic acid in the urine occurs in a small minority of cases (542,543).

Grossly, the tumor is rapidly growing pigmented (blue-black) soft tissue mass that displaces the upper lip. It may invade bone and orbit. Histologically, the tumor is not encapsulated and composed of dual population of small neuroblastic cells and larger melanin-containing epithelial cells in a dense fibrous stroma. The small neuroblastic cells are tightly arranged into small nests, surrounded by pigmented cells in an alveolar or tubular formation. FNA smears reveal a cellular aspirate with two different cell populations. The predominant cells consist of small, uniform neuroblastic cells with round nuclei and scanty to absent cytoplasm. The second population is oval to cuboidal large melanin-containing cells with eccentrically placed nuclei and moderate amount of cytoplasm. The granules of melanin pigment had a round to rod shape and stained brown with a Papanicolaou, bluish with DQ and black with the Masson-Fontana stain. The tumor is positive for HMB-45 and cytokeratin in the large pigmented cells and synaptophysin positive in the small round cells.

Melanocytoma (Magnocellular Nevus)

Melanocytoma (magnocellular nevus) is a rare, benign, heavily pigmented tumor that classically arises from the optic nerve; however, it might arise anywhere in the uveal tract (544,545). Melanocytomas occur primarily in heavily pigmented Caucasians and African-American adults. Melanocytomas can cause glaucoma either by direct spread into the anterior chamber angle (546), or massive dispersion of pigment into the angle from extensive necrosis of the tumor (547).

Only 15% of melanocytomas of optic disc enlarge over time (545), infiltrating the juxtapapillary choroids and optic nerve mimicking uveal melanomas (544). FNA examination reveals heavily pigmented polygonal cells with small vesicular nuclei and abundant cytoplasm totally packed with melanin granules (Fig. 128). Other cells appeared as branching dendritic cells with stubby cytoplasmic processes. Bleached preparation revealed the bland cytologic features of the melanocytic cells. Melanocytoma should be differentiated from uveal melanoma. The pigment granules in melanocytoma are much larger than those observed in uveal melanomas, and the cellular features of the bleached cytologic preparations are benign (548).

Benign melanocytic lesions (nevi) of the iris may grow to occlude the angle, leading to intractable glaucoma. The presence of large numbers of mucin containing goblet cells, sometimes aggregated into

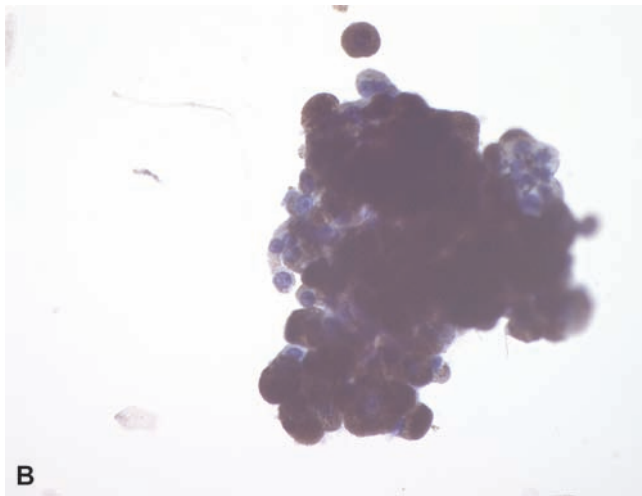
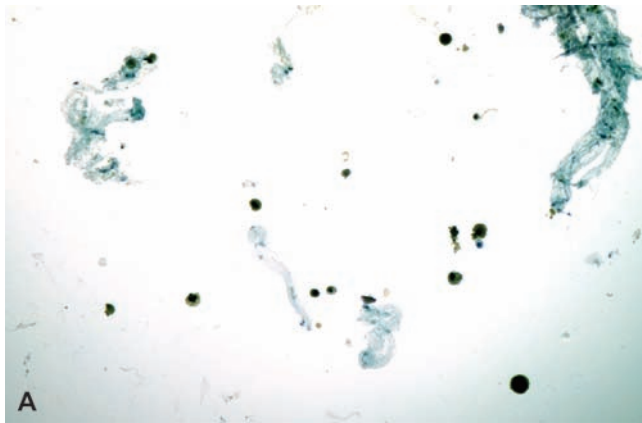


Figure 128 Melanocytoma (magnocellular nevus). FNAB reveals hypocellular smears with heavily pigmented polygonal cells, small vesicular nuclei, and abundant cytoplasm totally packed with melanin granules. Bleached preparation revealed the bland cytologic features of the melanocytic cells. [(A) DQ stain; magnification, 200 $\times$ (B) Papanicolaou stain; magnification, 600 $\times$].

cysts may suggest a mucoepidermoid tumor to the unwary. In addition, they may have an apparent rapid increase in size, leading to the clinical suspicion of melanoma. They may also involve the iris stroma extensively as well as having plaque-like extensions across the face of the iris (425). Unlike true melanoma cells, the nevus cells from these lesions do not have prominent nucleoli.

Malignant Melanoma

Malignant melanoma can occur in various ocular structures such as the eyelid, conjunctiva, uveal tract, and orbit. The great majority of ocular melanomas occur in the uveal tract (iris, ciliary body, and choroid) (548,549). However, choroid melanomas may rapidly enlarge, destroying visual function (549). Most conjunctival melanomas either arise *de novo* or within the

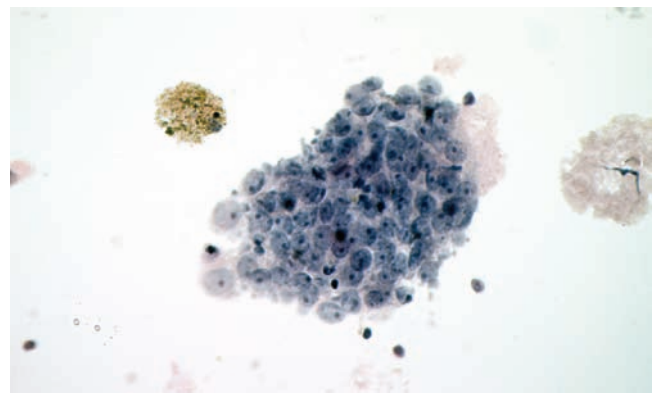


Figure 129 Malignant melanomas, Optic disc, plasmacytoid type. FNAB shows loosely cohesive malignant cells. Cells are epithelioid with high nuclear to cytoplasmic ratio and prominent nucleoli. Finely granular gray-black cytoplasmic pigment can be seen (Papanicolaou stain; magnification, 400 $\times$).

pre-malignant state known as primary acquired melanosis with atypia (550).

Melanocytic primary tumors of the conjunctiva can be diagnosed by scrape cytology and touch preparation cytology. Primary malignant melanomas should not be investigated by FNA cytology. However, metastatic deposits and occasional nodular melanomas will undergo FNAB. Smears from these lesions are usually highly cellular and often have a bloody background. Melanomas have a wide range of histologic and cytologic appearances, varying from spindle-shaped to plasmacytoid cells (Fig. 129). Woyke et al. (550) reported the following cytologic features that frequently occur in melanoma: (i) lack of cellular cohesion; (ii) binucleation or multinucleation of tumor giant cells; (iii) prominent nucleoli, intranuclear vacuoles, or pseudoinclusions. A subtype of melanoma is the predominantly spindle cell melanoma, in which the cells have long cytoplasmic processes and fusiform nuclei (Fig. 130). Occasionally lipoidal degeneration will lead to balloon cells (551). Positivity for S-100, Melan-A, and HMB-45 are helpful in establishing the diagnosis of malignant melanoma (552).

Aspirates of the anterior chamber in cases of malignant melanoma may contain pigment-laden macrophages or even melanoma cells. Melanophages should be differentiated from hyperplastic pigmented epithelial cells, derived from either the ciliary or iris-pigmented epithelial cells or from retinal-pigmented epithelium. Pigmented epithelial cells are typically cuboidal, with large individual melanin granules, whereas macrophages tend to have aggregates of melanin pigment present as clumps within lysosomes. Pigmented macrophages containing iron are seen in the anterior chamber and angle following intraocular hemorrhage and are often accompanied by "ghost" erythrocytes.

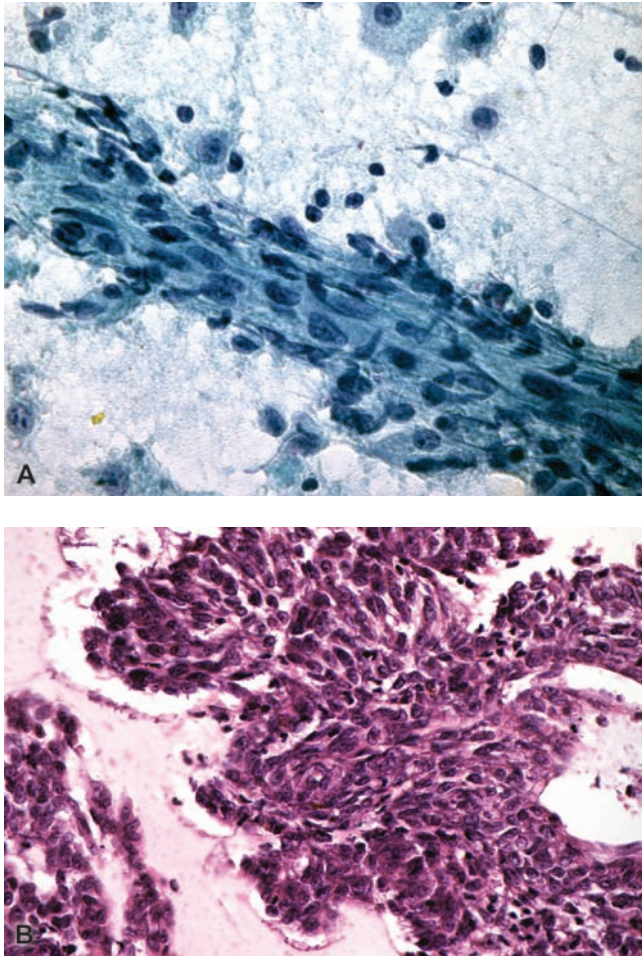


Figure 130 Malignant melanoma of ciliary body, spindle cell type. (A) The cells have long cytoplasmic processes and fusiform nuclei. Dyscohesive malignant cells are also seen. (B) Cell block and special stains confirm the diagnosis [(A) Papanicolaou stain; magnification, 400× (B) Cellblock H&E stain; magnification, 400×].

REFERENCES

1. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract* 2006; 12(1).
2. Ogilvie JB, Piatigorsky EJ, Clark OH. Current status of fine needle aspiration for thyroid nodules. *Adv Surg* 2006; 40:223–238.
3. Geisinger K. *Modern Cytopathology*. Philadelphia, PA: Churchill Livingstone, 2004.
4. Castro MR, Gharib H. Continuing controversies in the management of thyroid nodules. *Ann Intern Med* 7 2005; 142(11):926–931.
5. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med*, 1993; 118(4): 282–289.
6. Papanicolaou Society of Cytopathology Recommendations for Thyroid Fine Needle Aspiration. Diagnostic terminology and criteria for the cytologic diagnosis of

thyroid lesions. Available at: <http://www.papsociety.org/guidelines.html>. Accessed 2006.

7. Baloch ZW, Cibas ES, Clark DP, et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. *Cytojournal* 2008; 5:6.
8. Orell SR. *Fine Needle Aspiration Cytology*. 4th ed. Philadelphia, PA: Elsevier, 2005.
9. Baloch ZW, Hendreen S, Gupta PK, et al. Interinstitutional review of thyroid fine-needle aspirations: impact on clinical management of thyroid nodules. *Diagn Cytopathol* Oct 2001; 25(4):231–234.
10. Goellner JR, Gharib H, Grant CS, et al. Fine needle aspiration cytology of the thyroid, 1980 to 1986. *Acta Cytol* 1987; 31(5):587–590.
11. Nguyen GK, Ginsberg J, Crockford PM. Fine-needle aspiration biopsy cytology of the thyroid: its value and limitations in the diagnosis and management of solitary thyroid nodules. *Pathol Annu* 1991; 26(pt)1:63–91.
12. Hamburger JJ, Husain M. Semiquantitative criteria for fine-needle biopsy diagnosis: reduced false-negative diagnoses. *Diagn Cytopathol* 1988; 4(1):14–17.
13. Kini SR, Miller JM, Hamburger JJ, et al. Cytopathology of papillary carcinoma of the thyroid by fine needle aspiration. *Acta Cytol* 1980; 24(6):511–521.
14. Castro MR, Gharib H. Thyroid fine-needle aspiration biopsy: progress, practice, and pitfalls. *Endocr Pract* 2003; 9(2):128–136.
15. McHenry CR, Rosen IB, Walfish PG, et al. Influence of fine-needle aspiration biopsy and frozen section examination on the management of thyroid cancer. *Am J Surg* 1993; 166(4):353–356.
16. Schmidt T, Riggs MW, Speights VO Jr. Significance of nondiagnostic fine-needle aspiration of the thyroid. *South Med J* 1997; 90(12):1183–1186.
17. Wu HH, Jones JN, Osman J. Fine-needle aspiration cytology of the thyroid: ten years experience in a community teaching hospital. *Diagn Cytopathol* 2006; 34(2):93–96.
18. Danese D, Sciacchitano S, Farsetti A, et al. Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. *Thyroid* 1998; 8(1):15–21.
19. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. *Mayo Clin Proc* 1994; 69(1):44–49.
20. Baloch ZW, LiVolsi VA, Jain P, et al. Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules. *Diagn Cytopathol* 2003; 29(4):203–206.
21. Baloch ZW, LiVolsi VA. Post fine-needle aspiration histologic alterations of thyroid revisited. *Am J Clin Pathol* 1999; 112(3):311–316.
22. Flanagan MB, Ohori NP, Carty SE, et al. Repeat thyroid nodule fine-needle aspiration in patients with initial benign cytologic results. *Am J Clin Pathol* 2006; 125(5): 698–702.
23. Baloch ZW, Fleisher S, LiVolsi VA, et al. Diagnosis of “follicular neoplasm”: a gray zone in thyroid fine-needle aspiration cytology. *Diagn Cytopathol* 2002; 26(1): 41–44.
24. Reimann JD, Dorfman DM, Nose V. Carcinoma showing thymus-like differentiation of the thyroid (CASTLE): a comparative study: evidence of thymic differentiation and solid cell nest origin. *Am J Surg Pathol* 2006; 30(8):994–1001.
25. Tao LC. *Lung, Pleura, and Mediastinum*. Philadelphia, PA: Lippincott Williams & Wilkins, 1988.
26. Piacentini MG, Romano F, De Fina S, et al. Carcinoma of the neck showing thymic-like elements (CASTLE): report of a case and review of the literature. *Int J Surg Pathol* 2006; 14(2):171–175.

27. Baloch ZW, Tam D, Langer J, et al. Ultrasound-guided fine-needle aspiration biopsy of the thyroid: role of on-site assessment and multiple cytologic preparations. *Diagn Cytopathol* 2000; 23(6):425-429.
28. Biscotti CV, Hollow JA, Toddy SM, et al. ThinPrep versus conventional smear cytologic preparations in the analysis of thyroid fine-needle aspiration specimens. *Am J Clin Pathol* 1995; 104(2):150-153.
29. Layfield LJ, Wax T, Jones C. Cytologic distinction of goiterous nodules from morphologically normal thyroid: analyses of cytomorphologic features. *Cancer* 25 2003; 99(4): 217-222.
30. Baloch ZW, Sack MJ, Yu GH, et al. Fine-needle aspiration of thyroid: an institutional experience. *Thyroid* 1998; 8(7):565-569.
31. Soderstrom N, Nilsson G. Cytologic diagnosis of thyrotoxicosis. *Acta Med Scand* 1979; 205(4):263-265.
32. Centeno BA, Szyfelbein WM, Daniels GH, et al. Fine needle aspiration biopsy of the thyroid gland in patients with prior Graves' disease treated with radioactive iodine. Morphologic findings and potential pitfalls. *Acta Cytol* 1996; 40(6):1189-1197.
33. Anderson SR, Mandel S, LiVolsi VA, et al. Can cytomorphology differentiate between benign nodules and tumors arising in Graves' disease? *Diagn Cytopathol* 2004; 31(1): 64-67.
34. Kini SR, Miller JM, Hamburger JL, et al. Cytopathology of follicular lesions of the thyroid gland. *Diagn Cytopathol* 1985; 1(2):123-132.
35. Rout P, Shariff S. Diagnostic value of qualitative and quantitative variables in thyroid lesions. *Cytopathology* 1999; 10(3):171-179.
36. Kellman A. Thyroid cytology. *Thyroid* 2001; 11:271-277.
37. Barbaro D, Simi U, Lopane P, et al. Thyroid nodules with microfollicular findings reported on fine-needle aspiration: invariably surgical treatment? *Endocr Pract* 2001; 7(5):352-357.
38. Ersoz C, Firat P, Uguz A, et al. Fine-needle aspiration cytology of solitary thyroid nodules: how far can we go in rendering differential cytologic diagnoses? *Cancer* 2004; 102(5):302-307.
39. Goldstein RE, Netterville JL, Burkey B, et al. Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of thyroid nodules. *Ann Surg* 2002; 235(5):656-662; discussion 662-654.
40. Yang GC, Goldberg JD, Ye PX. Risk of malignancy in follicular neoplasms without nuclear atypia: statistical analysis of 397 thyroidectomies. *Endocr Pract* 2003; 9(6):510-516.
41. DeMay RM. The art and science of cytopathology. Chicago, IL: ASCP Press, 1996.
42. Basu D, Jayaram G. A logistic model for thyroid lesions. *Diagn Cytopathol* 1992; 8(1):23-27.
43. Harach HR, Soto MS, Zusman SB, et al. Parenchymatous thyroid nodules: a histocytological study of 31 cases from a goitrous area. *J Clin Pathol* 1992; 45(1):25-29.
44. Yang GC, Liebeskind D, Messina AV. Should cytopathologists stop reporting follicular neoplasms on fine-needle aspiration of the thyroid? *Cancer* 2003; 99(2):69-74.
45. Clary KM, Condel JL, Liu Y, et al. Interobserver variability in the fine needle aspiration biopsy diagnosis of follicular lesions of the thyroid gland. *Acta Cytol* 2005; 49(4):378-382.
46. Stelow EB, Bardales RH, Crary GS, et al. Interobserver variability in thyroid fine-needle aspiration interpretation of lesions showing predominantly colloid and follicular groups. *Am J Clin Pathol* 2005; 124(2):239-244.
47. Redman R, Yoder BJ, Massoll NA. Perceptions of diagnostic terminology and cytopathologic reporting of fine-needle aspiration biopsies of thyroid nodules: a survey of clinicians and pathologists. *Thyroid* 2006; 16(10): 1003-1008.
48. Piromalli D, Martelli G, Del Prato I, et al. The role of fine needle aspiration in the diagnosis of thyroid nodules: analysis of 795 consecutive cases. *J Surg Oncol* 1992; 50(4): 247-250.
49. Foppiani L, Tancredi M, Ansaldo GL, et al. Absence of histological malignancy in a patient cohort with follicular lesions on fine-needle aspiration. *J Endocrinol Invest* 2003; 26(1):29-34.
50. Kini SR, Miller JM, Hamburger JL. Cytopathology of Hurthle cell lesions of the thyroid gland by fine needle aspiration. *Acta Cytol* 1981; 25(6):647-652.
51. Kaur A, Jayaram G. Thyroid tumors: cytomorphology of papillary carcinoma. *Diagn Cytopathol* 1991; 7(5):462-468.
52. Miller TR, Abele JS, Greenspan FS. Fine-needle aspiration biopsy in the management of thyroid nodules. *West J Med* 1981; 134(3):198-205.
53. Kini SR. *Guides to Clinical Aspiration Biopsy Thyroid*. 2nd ed. New York, NY: Igaku-Shoin, 1996.
54. Miller TR, Bottles K, Holly EA, et al. A step-wise logistic regression analysis of papillary carcinoma of the thyroid. *Acta Cytol* 1986; 30(3):285-293.
55. Goellner JR, Johnson DA. Cytology of cystic papillary carcinoma of the thyroid. *Acta Cytol* 1982; 26(6):797-808.
56. Jayaram G, Kaur A. Cystic thyroid nodules harboring malignancy: a problem in fine needle aspiration cytodiagnosis. *Acta Cytol* 1989; 33(6):941-942.
57. Fulciniti F, Benincasa G, Vetrani A, et al. Follicular variant of papillary carcinoma: cytologic findings on FNAB samples-experience with 16 cases. *Diagn Cytopathol* 2001; 25(2):86-93.
58. Wu HH, Jones JN, Grzybicki DM, et al. Sensitive cytologic criteria for the identification of follicular variant of papillary thyroid carcinoma in fine-needle aspiration biopsy. *Diagn Cytopathol* 2003; 29(5):262-266.
59. Gupta S, Sodhani P, Jain S, et al. Morphologic spectrum of papillary carcinoma of the thyroid: role of cytology in identifying the variants. *Acta Cytol* 2004; 48(6):795-800.
60. Logani S, Osei SY, LiVolsi VA, et al. Fine-needle aspiration of follicular variant of papillary carcinoma in a hyperfunctioning thyroid nodule. *Diagn Cytopathol* 2001; 25(1):80-81.
61. Forrest CH, Frost FA, de Boer WB, et al. Medullary carcinoma of the thyroid: accuracy of diagnosis of fine-needle aspiration cytology. *Cancer* 1998; 84(5):295-302.
62. Papaparaskeva K, Nagel H, Droese M. Cytologic diagnosis of medullary carcinoma of the thyroid gland. *Diagn Cytopathol* 2000; 22(6):351-358.
63. Faquin WC, Powers CN. Aggressive forms of follicular-derived thyroid carcinoma. *Pathol Case Rev* 2003; 8(1): 25-33.
64. Faquin WC, Cibas ES, Renshaw AA. "Atypical" cells in fine-needle aspiration biopsy specimens of benign thyroid cysts. *Cancer* 25 2005; 105(2):71-79.
65. Renshaw AA. "Histiocytoid" cells in fine-needle aspirations of papillary carcinoma of the thyroid: frequency and significance of an under-recognized cytologic pattern. *Cancer* 25 2002; 96(4):240-243.
66. Silverman JF, Khazanie PG, Norris HT, et al. Parathyroid hormone (PTH) assay of parathyroid cysts examined by fine-needle aspiration biopsy. *Am J Clin Pathol* 1986; 86(6): 776-780.
67. Larson RS, Wick MR. Primary mucoepidermoid carcinoma of the thyroid: diagnosis by fine-needle aspiration biopsy. *Diagn Cytopathol* 1993; 9(4):438-443.
68. Baloch ZW, LiVolsi VA. *Pathology of the thyroid gland*. Philadelphia, PA: Churchill Livingstone, 2002.

69. LiVolsi VA, ed. *Surgical Pathology of the Thyroid* (Major Problems in Pathology, Vol. 22). Philadelphia, PA: WB Saunders, 1990.
70. Lennard TW, Wadehra V, Farndon JR. Fine needle aspiration biopsy in diagnosis of metastases to thyroid gland. *J R Soc Med* 1984; 77(3):196–197.
71. Michelow PM, Leiman G. Metastases to the thyroid gland: diagnosis by aspiration cytology. *Diagn Cytopathol* 1995; 13(3):209–213.
72. Halbauer M, Kardum-Skelin I, Vranesic D, et al. Aspiration cytology of renal-cell carcinoma metastatic to the thyroid. *Acta Cytol* 1991; 35(4):443–446.
73. Boutsos EP, Bedrossian CW, De Frias DV, et al. Thyroid plasmacytoma mimicking medullary carcinoma: a potential pitfall in aspiration cytology. *Diagn Cytopathol* 2000; 23(5):354–358.
74. Renshaw AA. *Aspiration Cytology: A Pattern Recognition Approach*. Philadelphia, PA: Elsevier, 2005.
75. Krishnamurthy S. Applications of molecular techniques to fine-needle aspiration biopsy. *Cancer* 2007; 111(2): 106–122.
76. Greaves TS, Olvera M, Florentine BD, et al. Follicular lesions of thyroid: a 5-year fine-needle aspiration experience. *Cancer* 2000; 90(6):335–341.
77. Hamberger B, Gharib H, Melton LJ III, et al. Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. *Am J Med* 1982; 73(3):381–384.
78. La Rosa GL, Belfiore A, Giuffrida D, et al. Evaluation of the fine needle aspiration biopsy in the preoperative selection of cold thyroid nodules. *Cancer* 1991; 67(8): 2137–2141.
79. Nam-Goong IS, Kim HY, Gong G, et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. *Clin Endocrinol (Oxf)* 2004; 60(1):21–28.
80. Katz AD, Dunkleman D. Needle aspiration of nonfunctioning parathyroid cysts. *Arch Surg* 1984; 119(3):307–308.
81. Layfield LJ. Fine needle aspiration cytology of cystic parathyroid lesions. A cytomorphologic overlap with cystic lesions of the thyroid. *Acta Cytol* 1991; 35(4):447–450.
82. Bondeson L, Bondeson AG, Nissborg A, et al. Cytopathological variables in parathyroid lesions: a study based on 1,600 cases of hyperparathyroidism. *Diagn Cytopathol* 1997; 16(6):476–482.
83. Friedman M, Shimaoka K, Lopez CA, et al. Parathyroid adenoma diagnosed as papillary carcinoma of thyroid on needle aspiration smears. *Acta Cytol* 1983; 27(3):337–340.
84. Mincione GP, Borrelli D, Cicchi P, et al. Fine needle aspiration cytology of parathyroid adenoma. A review of seven cases. *Acta Cytol* 1986; 30(1):65–69.
85. Batsakis JG, Sneige N, el-Naggar AK. Fine-needle aspiration of salivary glands: its utility and tissue effects. *Ann Otol Rhinol Laryngol* 1992; 101(2 pt 1):185–188.
86. Kern SB. Necrosis of a Warthin's tumor following fine needle aspiration. *Acta Cytol* 1988; 32(2):207–208.
87. Pabuccuoglu HU, Lebe B, Sarioglu S, et al. Infarction of pleomorphic adenoma: a rare complication of fine-needle aspiration obscuring definitive diagnosis. *Diagn Cytopathol* 2001; 24(4):301–303.
88. Balakrishnan K, Castling B, McMahon J, et al. Fine needle aspiration cytology in the management of a parotid mass: a two centre retrospective study. *Surgeon* 2005; 3(2):67–72.
89. Boccato P, Altavilla G, Blandamura S. Fine needle aspiration biopsy of salivary gland lesions. A reappraisal of pitfalls and problems. *Acta Cytol* 1998; 42(4):888–898.
90. Cohen EG, Patel SG, Lin O, et al. Fine-needle aspiration biopsy of salivary gland lesions in a selected patient population. *Arch Otolaryngol Head Neck Surg* 2004; 130(6): 773–778.
91. Das DK, Petkar MA, Al-Mane NM, et al. Role of fine needle aspiration cytology in the diagnosis of swellings in the salivary gland regions: a study of 712 cases. *Med Princ Pract* 2004; 13(2):95–106.
92. Qizilbash AH, Sianos J, Young JE, et al. Fine needle aspiration biopsy cytology of major salivary glands. *Acta Cytol* 1985; 29(4):503–512.
93. Frable MA, Frable WJ. Fine-needle aspiration biopsy of salivary glands. *Laryngoscope* 1991; 101(3):245–249.
94. Rajwanshi A, Gupta K, Gupta N, et al. Fine-needle aspiration cytology of salivary glands: diagnostic pitfalls–revisited. *Diagn Cytopathol* 2006; 34(8):580–584.
95. Heller KS, Dubner S, Chess Q, et al. Value of fine needle aspiration biopsy of salivary gland masses in clinical decision-making. *Am J Surg* 1992; 164(6):667–670.
96. Cohen MB, Reznicek MJ, Miller TR. Fine-needle aspiration biopsy of the salivary glands. *Pathol Annu* 1992; 27 Pt 2:213–245.
97. Layfield LJ, Gopez EV. Cystic lesions of the salivary glands: cytologic features in fine-needle aspiration biopsies. *Diagn Cytopathol* 2002; 27(4):197–204.
98. Stanley M. Salivary glands and other head and neck masses. In: Geisinger K, Silverman JF, eds. *Fine Needle Aspiration Cytology of Superficial Organs and Body Sites*. Philadelphia, PA: Churchill Livingstone, 1999:105–156.
99. O'Dwyer P, Farrar WB, James AG, et al. Needle aspiration biopsy of major salivary gland tumors: its value. *Cancer* 1986; 57(3):554–557.
100. Henry-Stanley MJ, Beneke J, Bardales RH, et al. Fine-needle aspiration of normal tissue from enlarged salivary glands: sialosis or missed target? *Diagn Cytopathol* 1995; 13(4):300–303.
101. Layfield LJ, Glasgow BJ, Goldstein Net al. Lipomatous lesions of the parotid gland. Potential pitfalls in fine needle aspiration biopsy diagnosis. *Acta Cytol* 1991; 35(5): 553–556.
102. Ascoli V, Albedi FM, De Blasii R, et al. Sialadenosis of the parotid gland: report of four cases diagnosed by fine-needle aspiration cytology. *Diagn Cytopathol* 1993; 9(2): 151–155.
103. Mooney EE, Dodd LG, Layfield LJ. Squamous cells in fine-needle aspiration biopsies of salivary gland lesions: potential pitfalls in cytologic diagnosis. *Diagn Cytopathol* 1996; 15(5):447–452.
104. Krane JF, Faquin WC. Salivary gland. In: Cibas ES, Ducatman BS, eds. *Cytology: Diagnostic Principles and Clinical Correlates*. Philadelphia, PA: WB Saunders, 2003.
105. Droese M. Cytological diagnosis of sialadenosis, sialadenitis, and parotid cysts by fine-needle aspiration biopsy. *Adv Otorhinolaryngol* 1981; 26:49–96.
106. Engzell U, Zajicek J. Aspiration biopsy of tumors of the neck. I. Aspiration biopsy and cytologic findings in 100 cases of congenital cysts. *Acta Cytol* 1970; 14(2):51–57.
107. Lampe HB, Cramer HM. Advances in the use of fine-needle aspiration cytology in the diagnosis of palpable lesions of the head and neck. *J Otolaryngol* 1991; 20(2): 108–116.
108. Layfield LJ, Tan P, Glasgow BJ. Fine-needle aspiration of salivary gland lesions. Comparison with frozen sections and histologic findings. *Arch Pathol Lab Med* 1987; 111(4): 346–353.
109. Heller KS, Attie JN, Dubner S. Accuracy of frozen section in the evaluation of salivary tumors. *Am J Surg* 1993; 166(4): 424–427.
110. Barnes L, Eveson JW, Reichart P, et al. eds. *Pathology and Genetics of Head and Neck Tumours (WHO Classification of Tumours)*. Lyon: IARC Press, 2005.
111. Elsheikh TM. Salivary gland aspiration cytology. In: Atkinson BF, Silverman JF, eds. *Atlas of Difficult*

- Diagnoses in Cytopathology. Philadelphia, PA: WB Saunders, 1998.
112. Stanley MW, Horwitz CA, Rollins SD, et al. Basal cell (monomorphic) and minimally pleomorphic adenomas of the salivary glands. Distinction from the solid (anaplastic) type of adenoid cystic carcinoma in fine-needle aspiration. *Am J Clin Pathol* 1996; 106(1):35–41.
 113. Elsheikh T, Bernacki EG. FNA cytology of salivary gland neoplasms with basaloid cell features. *Acta Cytol* 1995; 39:1027–1028.
 114. Hood IC, Qizilbash AH, Salama SS, et al. Basal-cell adenoma of parotid. Difficulty of differentiation from adenoid cystic carcinoma on aspiration biopsy. *Acta Cytol* 1983; 27(5):515–520.
 115. Hruban RH, Erozan YS, Zinreich SJ, et al. Fine-needle aspiration cytology of monomorphic adenomas. *Am J Clin Pathol* 1988; 90(1):46–51.
 116. Lopez JI, Ballestin C. Fine-needle aspiration cytology of a membranous basal cell adenoma arising in an intraparotid lymph node. *Diagn Cytopathol* 1993; 9(6):668–672.
 117. Philpott CM, Kendall C, Murty GE. Canalicular adenoma of the parotid gland. *J Laryngol Otol* 2005; 119(1):59–60.
 118. Hoang JT, Foss RD, Nowacki MR, et al. Basaloid squamous cell carcinoma and fine-needle aspiration: a potential diagnostic pitfall. *Otolaryngol Head Neck Surg* 1998; 119(6):655–657.
 119. Pisharodi LR. Basal cell adenocarcinoma of the salivary gland. Diagnosis by fine-needle aspiration cytology. *Am J Clin Pathol* 1995; 103(5):603–608.
 120. Cameron WR, Johansson L, Tennvall J. Small cell carcinoma of the parotid. Fine needle aspiration and immunochemical findings in a case. *Acta Cytol* 1990; 34(6):837–841.
 121. Domanski HA, Domanski AM. Cytology of pilomatrixoma (calcifying epithelioma of Malherbe) in fine needle aspirates. *Acta Cytol* 1997; 41(3):771–777.
 122. Wong MP, Yuen ST, Collins RJ. Fine-needle aspiration biopsy of pilomatrixoma: still a diagnostic trap for the unwary. *Diagn Cytopathol* 1994; 10(4):365–369 (discussion 369–370).
 123. Elsheikh TM, Bernacki EG Jr. Fine needle aspiration cytology of cellular pleomorphic adenoma. *Acta Cytol* 1996; 40(6):1165–1175.
 124. Klijanienko J, Vielh P. Fine-needle sampling of salivary gland lesions. IV. Review of 50 cases of mucoepidermoid carcinoma with histologic correlation. *Diagn Cytopathol* 1997; 17(2):92–98.
 125. Cohen MB, Fisher PE, Holly EA, et al. Fine needle aspiration biopsy diagnosis of mucoepidermoid carcinoma. Statistical analysis. *Acta Cytol* 1990; 34(1):43–49.
 126. Zajicek J, Eneroth CM, Jakobsson P. Aspiration biopsy of salivary gland tumors. VI. Morphologic studies on smears and histologic sections from mucoepidermoid carcinoma. *Acta Cytol* 1976; 20(1):35–41.
 127. Kumar N, Kapila K, Verma K. Fine needle aspiration cytology of mucoepidermoid carcinoma. A diagnostic problem. *Acta Cytol* 1991; 35(3):357–359.
 128. MacLeod CB, Frable WJ. Fine-needle aspiration biopsy of the salivary gland: problem cases. *Diagn Cytopathol* 1993; 9(2):216–224 (discussion 224–215).
 129. Evans HL, Luna MA. Polymorphous low-grade adenocarcinoma: a study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas. *Am J Surg Pathol* 2000; 24(10):1319–1328.
 130. Frierson HF Jr., Mills SE, Garland TA. Terminal duct carcinoma of minor salivary glands. A nonpapillary subtype of polymorphous low-grade adenocarcinoma. *Am J Clin Pathol* 1985; 84(1):8–14.
 131. Ritland F, Lubensky I, LiVolsi VA. Polymorphous low-grade adenocarcinoma of the parotid salivary gland. *Arch Pathol Lab Med* 1993; 117(12):1261–1263.
 132. Simpson RH, Clarke TJ, Sarsfield PT, et al. Polymorphous low-grade adenocarcinoma of the salivary glands: a clinicopathological comparison with adenoid cystic carcinoma. *Histopathology* 1991; 19(2):121–129.
 133. Gibbons D, Saboorian MH, Vuitch F, et al. Fine-needle aspiration findings in patients with polymorphous low grade adenocarcinoma of the salivary glands. *Cancer* 1999; 87(1):31–36.
 134. Klijanienko J, Vielh P. Salivary carcinomas with papillae: cytology and histology analysis of polymorphous low-grade adenocarcinoma and papillary cystadenocarcinoma. *Diagn Cytopathol* 1998; 19(4):244–249.
 135. Lucarini JW, Sciubba JJ, Khettry U, et al. Terminal duct carcinoma. Recognition of a low-grade salivary adenocarcinoma. *Arch Otolaryngol Head Neck Surg* 1994; 120(9):1010–1015.
 136. Layfield LJ, Glasgow BJ. Diagnosis of salivary gland tumors by fine-needle aspiration cytology: a review of clinical utility and pitfalls. *Diagn Cytopathol* 1991; 7(3):267–272.
 137. Takeda Y, Yamamoto H. Oral collision carcinoma: salivary duct carcinoma of minor salivary gland origin and squamous cell carcinoma of the oral mucosa. *J Oral Sci* 1999; 41(3):129–131.
 138. Snyder ML, Paulino AF. Hybrid carcinoma of the salivary gland: salivary duct adenocarcinoma adenoid cystic carcinoma. *Histopathology* 1999; 35(4):380–383.
 139. Anand A, Brockie ES. Cytomorphological features of salivary duct carcinoma ex pleomorphic adenoma: diagnosis by fine-needle aspiration biopsy with histologic correlation. *Diagn Cytopathol* 1999; 20(6):375–378.
 140. Kamio N, Tanaka Y, Mukai M, et al. A hybrid carcinoma: adenoid cystic carcinoma and salivary duct carcinoma of the salivary gland. An immunohistochemical study. *Virchows Arch* 1997; 430(6):495–500.
 141. Delgado R, Klimstra D, Albores-Saavedra J. Low grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern. *Cancer* 1996; 78(5):958–967.
 142. Brandwein MS, Kapadia SB, Gnepp DR. Salivary and lacrimal glands. In: Gnepp DR, ed. *Diagnostic Surgical Pathology of the Head and Neck*. Philadelphia, PA: WB Saunders, 2001.
 143. Tatemoto Y, Ohno A, Osaki T. Low malignant intraductal carcinoma on the hard palate: a variant of salivary duct carcinoma? *Eur J Cancer B Oral Oncol* 1996; 32B(4):275–277.
 144. Elsheikh TM, Bernacki EG Jr., Pisharodi L. Fine-needle aspiration cytology of salivary duct carcinoma. *Diagn Cytopathol* 1994; 11(1):47–51.
 145. Khurana KK, Pitman MB, Powers CN, et al. Diagnostic pitfalls of aspiration cytology of salivary duct carcinoma. *Cancer* 1997; 81(6):373–378.
 146. Chen KT. Cytology of salivary duct carcinoma. *Diagn Cytopathol* 2000; 22(2):132–135.
 147. Auclair PL, Ellis GL, Gnepp DR. *Surgical Pathology of the Salivary Glands*. Philadelphia, PA: WB Saunders, 1991.
 148. Frierson HF Jr., Covell JL, Mills SE. Fine-needle aspiration cytology of terminal duct carcinoma of minor salivary gland. *Diagn Cytopathol* 1987; 3(2):159–162.
 149. Klijanienko J, Vielh P. Fine-needle sample of salivary gland lesions. V: Cytology of 22 cases of acinic cell carcinoma with histologic correlation. *Diagn Cytopathol* 1997; 17(5):347–352.
 150. Sauer T, Jebsen PW, Olsholt R. Cytologic features of papillary-cystic variant of acinic-cell adenocarcinoma: a case report. *Diagn Cytopathol* 1994; 10(1):30–32.

151. Nagel H, Laskawi R, Buter JJ, et al. Cytologic diagnosis of acinic-cell carcinoma of salivary glands. *Diagn Cytopathol* 1997; 16(5):402-412.
152. Laforga JB, Aranda FI. Oncocytic carcinoma of parotid gland: fine-needle aspiration and histologic findings. *Diagn Cytopathol* 1994; 11(4):376-379.
153. Rajan PB, Wadehra V, Hemming JD, et al. Fine needle aspiration cytology of malignant oncocytoma of the parotid gland: a case report. *Cytopathology* 1994; 5(2):110-113.
154. Seifert G, Hennings K, Caselitz J. Metastatic tumors to the parotid and submandibular glands—analysis and differential diagnosis of 108 cases. *Pathol Res Pract* 1986; 181(6): 684-692.
155. Batsakis JG, Bautina E. Metastases to major salivary glands. *Ann Otol Rhinol Laryngol* 1990; 99(6 pt 1):501-503.
156. Zhang C, Cohen JM, Cangiarella JF, et al. Fine-needle aspiration of secondary neoplasms involving the salivary glands. A report of 36 cases. *Am J Clin Pathol* 2000; 113(1): 21-28.
157. Chen KT, Hafez GR. Infiltrating salivary duct carcinoma. A clinicopathologic study of five cases. *Arch Otolaryngol* 1981; 107(1):37-39.
158. Hoang MP, Callender DL, Sola Gallego JJ, et al. Molecular and biomarker analyses of salivary duct carcinomas: comparison with mammary duct carcinoma. *Int J Oncol* 2001; 19(4):865-871.
159. Moriki T, Ueta S, Takahashi T, et al. Salivary duct carcinoma: cytologic characteristics and application of androgen receptor immunostaining for diagnosis. *Cancer* 2001; 93(5):344-350.
160. Wick MR, Ockner DM, Mills SE, et al. Homologous carcinomas of the breasts, skin, and salivary glands. A histologic and immunohistochemical comparison of ductal mammary carcinoma, ductal sweat gland carcinoma, and salivary duct carcinoma. *Am J Clin Pathol* 1998; 109(1):75-84.
161. Wick MR, Lillemoe TJ, Copland GT, et al. Gross cystic disease fluid protein-15 as a marker for breast cancer: immunohistochemical analysis of 690 human neoplasms and comparison with alpha-lactalbumin. *Hum Pathol* 1989; 20(3):281-287.
162. Fan CY, Wang J, Barnes EL. Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma: an immunohistochemical analysis of 13 cases and review of the literature. *Am J Surg Pathol* 2000; 24(4): 579-586.
163. James GK, Pudek M, Berean KW, et al. Salivary duct carcinoma secreting prostate-specific antigen. *Am J Clin Pathol* 1996; 106(2):242-247.
164. Garcia-Bonafe M, Catala I, Tarragona J, et al. Cytologic diagnosis of salivary duct carcinoma: a review of seven cases. *Diagn Cytopathol* 1998; 19(2):120-123.
165. Nikitakis NG, Tosios KI, Papanikolaou VS, et al. Immunohistochemical expression of cytokeratins 7 and 20 in malignant salivary gland tumors. *Mod Pathol* 2004; 17(4): 407-415.
166. Ordóñez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. *Adv Anat Pathol* 2000; 7(2): 123-127.
167. Reis-Filho JS, Carrilho C, Valenti C, et al. Is TTF1 a good immunohistochemical marker to distinguish primary from metastatic lung adenocarcinomas? *Pathol Res Pract* 2000; 196(12):835-840.
168. Schelkun PM, Grundy WG. Fine-needle aspiration biopsy of head and neck lesions. *J Oral Maxillofac Surg* 1991; 49(3): 262-267.
169. Miliauskas JR, Orell SR. Fine-needle aspiration cytological findings in five cases of epithelial-myoepithelial carcinoma of salivary glands. *Diagn Cytopathol* 2003; 28(3):163-167.
170. Wax T, Layfield LJ. Epithelial-myoepithelial cell carcinoma of the parotid gland: a case report and comparison of cytologic features with other stromal, epithelial, and myoepithelial cell containing lesions of the salivary glands. *Diagn Cytopathol* 1996; 14(4):298-304.
171. Izquierdo R, Arekat MR, Knudson PE, et al. Comparison of palpation-guided versus ultrasound-guided fine-needle aspiration biopsies of thyroid nodules in an outpatient endocrinology practice. *Endocr Pract* 2006; 12(6):609-614.
172. Kljanić J, Vielh P. Fine-needle sampling of salivary gland lesions. VII. Cytology and histology correlation of five cases of epithelial-myoepithelial carcinoma. *Diagn Cytopathol* 1998; 19(6):405-409.
173. Gnepp D, ed. *Diagnostic Surgical Pathology of the Head and Neck*. Philadelphia, PA: WB Saunders, 2001.
174. Auclair PL, Ellis GL, Stanley MW. Minor and major salivary glands. In: Silverberg S, DeLellis RA, Frable WJ, et al., eds. *Silverberg's Principles and Practice of Surgical Pathology and Cytopathology*. Philadelphia, PA: Churchill Livingstone, 2006:1245-1248.
175. Huvois A, Paulino A FG. Salivary glands. In: Mills S, ed. *Sternberg's Diagnostic Surgical Pathology*. 4 ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2004:950-952.
176. Gilcrease MZ, Guzman-Paz M, Froberg K, et al. Salivary duct carcinoma: is a specific diagnosis possible by fine needle aspiration cytology? *Acta Cytol* 1998; 42(6): 1389-1396.
177. Harris NL. Lymphoid proliferations of the salivary glands. *Am J Clin Pathol* 1999; 111(1 suppl 1):S94-S103.
178. Young NA, Al-Saleem T. Diagnosis of lymphoma by fine-needle aspiration cytology using the revised European-American classification of lymphoid neoplasms. *Cancer* 25 1999; 87(6):325-345.
179. Safneck JR, Ravinsky E, Yazdi HM, et al. Fine needle aspiration biopsy findings in lymphoepithelial carcinoma of salivary gland. *Acta Cytol* 1997; 41(4):1023-1030.
180. Gunhan O, Celasun B, Safali M, et al. Fine needle aspiration cytology of malignant lymphoepithelial lesion of the salivary gland. A report of two cases. *Acta Cytol* 1994; 38(5): 751-754.
181. Elliott JN, Oertel YC. Lymphoepithelial cysts of the salivary glands. Histologic and cytologic features. *Am J Clin Pathol* 1990; 93(1):39-43.
182. Chai C, Dodd LG, Glasgow BJ, et al. Salivary gland lesions with a prominent lymphoid component: cytologic findings and differential diagnosis by fine-needle aspiration biopsy. *Diagn Cytopathol* 1997; 17(3):183-190.
183. Lowhagan T, Tani EM. Salivary gland and rare head and neck lesions. In: Bibo M, ed. *Comprehensive Cytopathology*. Pennsylvania, PA: WB Saunders, 1991:621-640.
184. Qizilbash A, Young JEM. *Guides to Clinical aspiration biopsy: Head and Neck*. 2nd ed. New York, NY: Igaku Shoin, 1996.
185. Kapadia SB, Dusenbery D, Dekker A. Fine needle aspiration of pleomorphic adenoma and adenoid cystic carcinoma of salivary gland origin. *Acta Cytol* 1997; 41(2):487-492.
186. Kljanić J, Vielh P. Fine-needle sampling of salivary gland lesions. I. Cytology and histology correlation of 412 cases of pleomorphic adenoma. *Diagn Cytopathol* 1996; 14(3):195-200.
187. Young JA. Diagnostic problems in fine needle aspiration cytopathology of the salivary glands. *J Clin Pathol* 1994; 47(3):193-198.
188. Chan MK, McGuire LJ, King W, et al. Cytodiagnosis of 112 salivary gland lesions. Correlation with histologic and frozen section diagnosis. *Acta Cytol* 1992; 36(3):353-363.
189. Jayaram N, Ashim D, Rajwanshi A, et al. The value of fine-needle aspiration biopsy in the cytodiagnosis of salivary gland lesions. *Diagn Cytopathol* 1989; 5(4):349-354.

190. Orell SR, Nettle WJ. Fine needle aspiration biopsy of salivary gland tumours. Problems and pitfalls. *Pathology* 1988; 20(4):332-337.
191. Viguer JM, Vicandi B, Jimenez-Heffernan JA, et al. Fine needle aspiration cytology of pleomorphic adenoma. An analysis of 212 cases. *Acta Cytol* 1997; 41(3):786-794.
192. Geisinger KR, Reynolds GD, Vance RP, et al. Adenoid cystic carcinoma arising in a pleomorphic adenoma of the parotid gland. An aspiration cytology and ultrastructural study. *Acta Cytol* 1985; 29(4):522-526.
193. Chhieng DC, Cohen JM, Cangiarella JF. Fine-needle aspiration of spindle cell and mesenchymal lesions of the salivary glands. *Diagn Cytopathol* 2000; 23(4):253-259.
194. Franquemont DW, Mills SE. Plasmacytoid monomorphic adenoma of salivary glands. Absence of myogenous differentiation and comparison to spindle cell myoepithelioma. *Am J Surg Pathol* 1993; 17(2):146-153.
195. Schultenover SJ, McDonald EC, Ramzy I. Hyaline-cell pleomorphic adenoma. Diagnosis by fine needle aspiration biopsy. *Acta Cytol* 1984; 28(5):593-597.
196. Dardick I, Cavell S, Boivin M, et al. Salivary gland myoepithelioma variants. Histological, ultrastructural, and immunocytological features. *Virchows Arch A Pathol Anat Histopathol* 1989; 416(1):25-42.
197. Di Palma S, Guzzo M. Malignant myoepithelioma of salivary glands: clinicopathological features of ten cases. *Virchows Arch A Pathol Anat Histopathol* 1993; 423(5):389-396.
198. Jacobs JC. Low grade mucoepidermoid carcinoma ex pleomorphic adenoma. A diagnostic problem in fine needle aspiration biopsy. *Acta Cytol* 1994; 38(1):93-97.
199. Serrano Egea A, Martinez Gonzalez MA, Perez Barrios A, et al. Usefulness of light microscopy in lymph node fine needle aspiration biopsy. *Acta Cytol* 2002; 46(2):364-368.
200. Steel BL, Schwartz MR, Ramzy I. Fine needle aspiration biopsy in the diagnosis of lymphadenopathy in 1,103 patients. Role, limitations and analysis of diagnostic pitfalls. *Acta Cytol* 1995; 39(1):76-81.
201. Prasad RR, Narasimhan R, Sankaran V, et al. Fine-needle aspiration cytology in the diagnosis of superficial lymphadenopathy: an analysis of 2,418 cases. *Diagn Cytopathol* 1996; 15(5):382-386.
202. Martins MR, Santos Gda C. Fine-needle aspiration cytology in the diagnosis of superficial lymphadenopathy: a 5-year Brazilian experience. *Diagn Cytopathol* 2006; 34(2):130-134.
203. Pilotti S, Di Palma S, Alasio L, et al. Diagnostic assessment of enlarged superficial lymph nodes by fine needle aspiration. *Acta Cytol* 1993; 37(6):853-866.
204. Wakely PE Jr. Fine-needle aspiration cytopathology in diagnosis and classification of malignant lymphoma: accurate and reliable? *Diagn Cytopathol* 2000; 22(2):120-125.
205. Jaffe ES, Harris NL, Stein M, eds. *Pathology and Genetics of Tumours and Haematopoietic and Lymphoid Tissues* (World Health Organization Classification of Tumors). Lyon: IARC, 2001.
206. Fulciniti F, Vetrani A, Zeppa P, et al. Hodgkin's disease: diagnostic accuracy of fine needle aspiration: a report based on 62 consecutive cases. *Cytopathology* 1994; 5(4):226-233.
207. Dong HY, Harris NL, Preffer FI, et al. Fine-needle aspiration biopsy in the diagnosis and classification of primary and recurrent lymphoma: a retrospective analysis of the utility of cytomorphology and flow cytometry. *Mod Pathol* 2001; 14(5):472-481.
208. Tarantino DR, McHenry CR, Strickland T, et al. The role of fine-needle aspiration biopsy and flow cytometry in the evaluation of persistent neck adenopathy. *Am J Surg* 1998; 176(5):413-417.
209. Young NA, Al-Saleem TI, Al-Saleem Z, et al. The value of transformed lymphocyte count in subclassification of non-Hodgkin's lymphoma by fine-needle aspiration. *Am J Clin Pathol* 1997; 108(2):143-151.
210. Young NA, Al-Saleem TI, Ehya H, et al. Utilization of fine-needle aspiration cytology and flow cytometry in the diagnosis and subclassification of primary and recurrent lymphoma. *Cancer* 25 1998; 84(4):252-261.
211. Singh HK, Volmar KE, Elsheikh TM, et al. The diagnostic utility of fine needle aspiration biopsy of soft tissue sarcomas in the core needle biopsy era. *Pathol Case Rev* 2007; 12(1):36-43.
212. Volmar KE, Singh HK, Gong JZ. The advantages and limitations of the role of core needle and fine needle aspiration biopsy of lymph nodes in the modern era: Hodgkin and non-Hodgkin lymphomas and metastatic disease. *Pathol Case Rev* 2007; 12(1):10-26.
213. Geisinger KR, Rainer RO, Field AS. Lymph nodes. In: Geisinger KR, Silverman JF, eds. *Fine Needle Aspiration Cytology of Superficial Organs and Body Sites*. New York, NY: Churchill-Livingstone, 1999:1-49.
214. van de Schoot L, Aronson DC, Behrendt H, et al. The role of fine-needle aspiration cytology in children with persistent or suspicious lymphadenopathy. *J Pediatr Surg* 2001; 36(1):7-11.
215. Daskalopoulou D, Harhalakis N, Maouni N, et al. Fine needle aspiration cytology of non-Hodgkin's lymphomas: a morphologic and immunophenotypic study. *Acta Cytol* 1995; 39(2):180-186.
216. Liu K, Stern RC, Rogers RT, et al. Diagnosis of hematopoietic processes by fine-needle aspiration in conjunction with flow cytometry: a review of 127 cases. *Diagn Cytopathol* 2001; 24(1):1-10.
217. Meda BA, Buss DH, Woodruff RD, et al. Diagnosis and subclassification of primary and recurrent lymphoma: the usefulness and limitations of combined fine-needle aspiration cytomorphology and flow cytometry. *Am J Clin Pathol* 2000; 113(5):688-699.
218. Nasuti JF, Yu G, Boudousquie A, Gupta P. Diagnostic value of lymph node fine needle aspiration cytology: an institutional experience of 387 cases observed over a 5-year period. *Cytopathology* 2000; 11(1):18-31.
219. Stewart CJ, Duncan JA, Farquharson M, et al. Fine needle aspiration cytology diagnosis of malignant lymphoma and reactive lymphoid hyperplasia. *J Clin Pathol* 1998; 51(3):197-203.
220. Chhieng DC, Cangiarella JF, Symmans WF, et al. Fine-needle aspiration cytology of Hodgkin disease: a study of 89 cases with emphasis on false-negative cases. *Cancer* 25 2001; 93(1):52-59.
221. Jimenez-Heffernan JA, Vicandi B, Lopez-Ferrer P, et al. Value of fine needle aspiration cytology in the initial diagnosis of Hodgkin's disease: analysis of 188 cases with an emphasis on diagnostic pitfalls. *Acta Cytol* 2001; 45(3):300-306.
222. Moreland WS, Geisinger KR. Utility and outcomes of fine-needle aspiration biopsy in Hodgkin's disease. *Diagn Cytopathol* 2002; 26(5):278-282.
223. Frable WJ, Kardos TF. Fine needle aspiration biopsy: applications in the diagnosis of lymphoproliferative diseases. *Am J Surg Pathol* 1988; 12(suppl 1):62-72.
224. Stewart CJ, Farquharson MA, Kerr T, et al. Immunoglobulin light chain mRNA detected by in situ hybridisation in diagnostic fine needle aspiration cytology specimens. *J Clin Pathol* 1996; 49(9):749-754.
225. Ben-Yehuda D, Polliack A, Okon E, et al. Image-guided core-needle biopsy in malignant lymphoma: experience with 100 patients that suggests the technique is reliable. *J Clin Oncol* 1996; 14(9):2431-2434.

226. Pappa VI, Hussain HK, Reznek RH, et al. Role of image-guided core-needle biopsy in the management of patients with lymphoma. *J Clin Oncol* 1996; 14(9):2427–2430.
227. Wotherspoon AC, Norton AJ, Lees WR, et al. Diagnostic fine needle core biopsy of deep lymph nodes for the diagnosis of lymphoma in patients unfit for surgery. *J Pathol* 1989; 158(2):115–121.
228. Gong JZ, Snyder MJ, Lagoo AS, et al. Diagnostic impact of core-needle biopsy on fine-needle aspiration of non-Hodgkin lymphoma. *Diagn Cytopathol* 2004; 31(1):23–30.
229. Jeffers MD, Milton J, Herriot R, et al. Fine needle aspiration cytology in the investigation on non-Hodgkin's lymphoma. *J Clin Pathol* 1998; 51(3):189–196.
230. Gong JZ, Williams DC Jr., Liu K, et al. Fine-needle aspiration in non-Hodgkin lymphoma: evaluation of cell size by cytomorphology and flow cytometry. *Am J Clin Pathol* 2002; 117(6):880–888.
231. Nicol TL, Silberman M, Rosenthal DL, et al. The accuracy of combined cytopathologic and flow cytometric analysis of fine-needle aspirates of lymph nodes. *Am J Clin Pathol* 2000; 114(1):18–28.
232. Safley AM, Buckley PJ, Creager AJ, et al. The value of fluorescence in situ hybridization and polymerase chain reaction in the diagnosis of B-cell non-Hodgkin lymphoma by fine-needle aspiration. *Arch Pathol Lab Med* 2004; 128(12):1395–1403.
233. Caraway NP, Gu J, Lin P, et al. The utility of interphase fluorescence in situ hybridization for the detection of the translocation t(11;14)(q13;q32) in the diagnosis of mantle cell lymphoma on fine-needle aspiration specimens. *Cancer* 2005; 105(2):110–118.
234. Torlakovic E, Berner A, Risberg B. Detection of immunoglobulin heavy chain gene rearrangements by polymerase chain reaction analysis on lymph node imprints and fine-needle aspirate smears: a comparison of five different imprint preparations. *Diagn Cytopathol* 1999; 20(6):333–338.
235. Ruschenburg I, Schlott T, Linke B, et al. Automated molecular genetic DNA analysis for detecting B-cell non-Hodgkin's lymphoma in cytologic specimens. *Anal Quant Cytol Histol* 1997; 19(3):255–263.
236. Goy A, Stewart J, Barkoh BA, et al. The feasibility of gene expression profiling generated in fine-needle aspiration specimens from patients with follicular lymphoma and diffuse large B-cell lymphoma. *Cancer* 2006; 108(1):10–20.
237. Hecht JL, Aster JC. Molecular biology of Burkitt's lymphoma. *J Clin Oncol* 2000; 18(21):3707–3721.
238. Kaleem Z, White G, Vollmer RT. Critical analysis and diagnostic usefulness of limited immunophenotyping of B-cell non-Hodgkin lymphomas by flow cytometry. *Am J Clin Pathol* 2001; 115(1):136–142.
239. Kinney MC, Kadin ME. The pathologic and clinical spectrum of anaplastic large cell lymphoma and correlation with ALK gene dysregulation. *Am J Clin Pathol* 1999; 111(1 suppl 1):S56–S67.
240. McCluggage WG, Anderson N, Herron B, Caughley L. Fine needle aspiration cytology, histology and immunohistochemistry of anaplastic large cell Ki-1-positive lymphoma. A report of three cases. *Acta Cytol* 1996; 40(4):779–785.
241. Sgrignoli A, Abati A. Cytologic diagnosis of anaplastic large cell lymphoma. *Acta Cytol* 1997; 41(4):1048–1052.
242. Zakowski MF, Feiner H, Finfer M, et al. Cytology of extranodal Ki-1 anaplastic large cell lymphoma. *Diagn Cytopathol* 1996; 14(2):155–161.
243. Aljajeh IA, Das DK, Krajci D. Ki-1-positive anaplastic large cell lymphoma initially diagnosed as Hodgkin's disease by fine needle aspiration (FNA) cytology. *Cytopathology* 1995; 6(4):226–235.
244. Bizjak-Schwarzbartl M. Large cell anaplastic Ki-1+ non-Hodgkin's lymphoma vs. Hodgkin's disease in fine needle aspiration biopsy samples. *Acta Cytol* 1997; 41(2):351–356.
245. Chhieng DC, Cohen JM, Cangiarella JF. Cytology and immunophenotyping of low- and intermediate-grade B-cell non-Hodgkin's lymphomas with a predominant small-cell component: a study of 56 cases. *Diagn Cytopathol* 2001; 24(2):90–97.
246. Shin HJ, Caraway NP, Katz RL. Cytomorphologic spectrum of small lymphocytic lymphoma in patients with an accelerated clinical course. *Cancer* 2003; 99(5):293–300.
247. Caraway NP, Du Y, Zhang HZ, et al. Numeric chromosomal abnormalities in small lymphocytic and transformed large cell lymphomas detected by fluorescence in situ hybridization of fine-needle aspiration biopsies. *Cancer* 2000; 90(2):126–132.
248. Rassidakis GZ, Tani E, Svedmyr E, et al. Diagnosis and subclassification of follicle center and mantle cell lymphomas on fine-needle aspirates: a cytologic and immunocytochemical approach based on the Revised European-American Lymphoma (REAL) classification. *Cancer* 1999; 87(4):216–223.
249. Murphy BA, Meda BA, Buss DH, et al. Marginal zone and mantle cell lymphomas: assessment of cytomorphology in subtyping small B-cell lymphomas. *Diagn Cytopathol* 2003; 28(3):126–130.
250. Hughes JH, Caraway NP, Katz RL. Blastic variant of mantle-cell lymphoma: cytomorphologic, immunocytochemical, and molecular genetic features of tissue obtained by fine-needle aspiration biopsy. *Diagn Cytopathol* 1998; 19(1):59–62.
251. Bentz JS, Rowe LR, Anderson SR, et al. Rapid detection of the t(11;14) translocation in mantle cell lymphoma by interphase fluorescence in situ hybridization on archival cytopathologic material. *Cancer* 2004; 102(2):124–131.
252. Gong Y, Caraway N, Gu J, et al. Evaluation of interphase fluorescence in situ hybridization for the t(14;18)(q32;q21) translocation in the diagnosis of follicular lymphoma on fine-needle aspirates: a comparison with flow cytometry immunophenotyping. *Cancer* 2003; 99(6):385–393.
253. Kim SE, Kim SH, Lim BJ, et al. Fine needle aspiration cytology of small cell variant of anaplastic large cell lymphoma: a case report. *Acta Cytol* 2004; 48(2):254–258.
254. Zhang JR, Raza AS, Greaves TS, Cobb CJ. Fine-needle aspiration diagnosis of Hodgkin lymphoma using current WHO classification: re-evaluation of cases from 1999–2004 with new proposals. *Diagn Cytopathol* 2006; 34(6):397–402.
255. Grenko RT, Shabb NS. Metastatic nasopharyngeal carcinoma: cytologic features of 18 cases. *Diagn Cytopathol* 1991; 7(6):562–566.
256. De Jong SA, Demeter JG, Jarosz H, et al. Primary papillary thyroid carcinoma presenting as cervical lymphadenopathy: the operative approach to the "lateral aberrant thyroid". *Am Surg* 1993; 59(3):172–176 (discussion 176–177).
257. Stani J. Cytologic diagnosis of reactive lymphadenopathy in fine needle aspiration biopsy specimens. *Acta Cytol* 1987; 31(1):8–13.
258. Creager AJ, Geisinger KR, Bergman S. Neutrophil-rich Ki-1-positive anaplastic large cell lymphoma: a study by fine-needle aspiration biopsy. *Am J Clin Pathol* 2002; 117(5):709–715.
259. Tani E, Ersoz C, Svedmyr E, Skoog L. Fine-needle aspiration cytology and immunocytochemistry of Hodgkin's disease, suppurative type. *Diagn Cytopathol* 1998; 18(6):437–440.
260. Ellison E, Lapuerta P, Martin SE. Fine needle aspiration diagnosis of mycobacterial lymphadenitis. Sensitivity and

- predictive value in the United States. *Acta Cytol* 1999; 43(2):153–157.
261. Maygarden SJ, Flanders EL. Mycobacteria can be seen as “negative images” in cytology smears from patients with acquired immunodeficiency syndrome. *Mod Pathol* 1989; 2(3):239–243.
 262. Gupta RK. Fine needle aspiration cytodiagnosis of toxoplastic lymphadenitis. *Acta Cytol* 1997; 41(4):1031–1034.
 263. Argyle JC, Schumann GB, Kjeldsberg CR, et al. Identification of a toxoplasma cyst by fine-needle aspiration. *Am J Clin Pathol* 1983; 80(2):256–258.
 264. Christ ML, Feltes-Kennedy M. Fine needle aspiration cytology of toxoplastic lymphadenitis. *Acta Cytol* 1982; 26(4):425–428.
 265. Viguer JM, Jimenez-Heffernan JA, Lopez-Ferrer P, et al. Fine needle aspiration of toxoplastic (Piringer-Kuchinka) lymphadenitis: a cytohistologic correlation study. *Acta Cytol* 2005; 49(2):139–143.
 266. Zaharopoulos P. Demonstration of parasites in toxoplasma lymphadenitis by fine-needle aspiration cytology: report of two cases. *Diagn Cytopathol* 2000; 22(1):11–15.
 267. Volmar KE, Singh HK, Gong JZ. Fine needle aspiration biopsy of lymph nodes in the modern era: reactive lymphadenopathies. *Pathol Case Rev* 2007; 12(1):27–35.
 268. Jayaram N, Ramaprasad AV, Chethan M, et al. Toxoplasma lymphadenitis. Analysis of cytologic and histopathologic criteria and correlation with serologic tests. *Acta Cytol* 1997; 41(3):653–658.
 269. Silverman JF. Fine needle aspiration cytology of cat scratch disease. *Acta Cytol* 1985; 29(4):542–547.
 270. Donnelly A, Hendricks G, Martens S, et al. Cytologic diagnosis of cat scratch disease (CSD) by fine-needle aspiration. *Diagn Cytopathol* 1995; 13(2):103–106.
 271. Stastny JF, Wakely PE Jr., Frable WJ. Cytologic features of necrotizing granulomatous inflammation consistent with cat-scratch disease. *Diagn Cytopathol* 1996; 15(2):108–115.
 272. Stanley MW, Steeper TA, Horwitz CA, et al. Fine-needle aspiration of lymph nodes in patients with acute infectious mononucleosis. *Diagn Cytopathol* 1990; 6(5):323–329.
 273. Kardos TF, Kornstein MJ, Frable WJ. Cytology and immunocytology of infectious mononucleosis in fine needle aspirates of lymph nodes. *Acta Cytol* 1988; 32(5):722–726.
 274. Kardos TF, Sprague RI, Wakely PE Jr., et al. Fine-needle aspiration biopsy of lymphoblastic lymphoma and leukemia: a clinical, cytologic, and immunologic study. *Cancer* 1987; 60(10):2448–2453.
 275. Deshpande V, Verma K. Fine needle aspiration (FNA) cytology of Rosai Dorfman disease. *Cytopathology* 1998; 9(5):329–335.
 276. Deshpande AH, Nayak S, Munshi MM. Cytology of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). *Diagn Cytopathol* 2000; 22(3):181–185.
 277. Layfield LJ. Fine needle aspiration cytologic findings in a case of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman syndrome). *Acta Cytol* 1990; 34(6):767–770.
 278. Ruggiero A, Attina G, Maurizi P, et al. Rosai-Dorfman disease: two case reports and diagnostic role of fine-needle aspiration cytology. *J Pediatr Hematol Oncol* 2006; 28(2):103–106.
 279. Kakkar S, Kapila K, Verma K. Langerhans cell histiocytosis in lymph nodes. Cytomorphologic diagnosis and pitfalls. *Acta Cytol* 2001; 45(3):327–332.
 280. Tong TR, Chan OW, Lee KC. Diagnosing Kikuchi disease on fine needle aspiration biopsy: a retrospective study of 44 cases diagnosed by cytology and 8 by histopathology. *Acta Cytol* 2001; 45(6):953–957.
 281. Tsang WY, Chan JK. Fine-needle aspiration cytologic diagnosis of Kikuchi’s lymphadenitis. A report of 27 cases. *Am J Clin Pathol* 1994; 102(4):454–458.
 282. Geisinger KR, Silverman JF, Wakely PE Jr. *Pediatric Cytopathology*. 1st ed. Chicago, IL: American Society of Clinical Pathologists, 1994.
 283. Gonzalez-Campora R, Otal-Salaverri C, Hevia-Vazquez A, et al. Fine needle aspiration in myxoid tumors of the soft tissues. *Acta Cytol* 1990; 34(2):179–191.
 284. Singh HK, Kilpatrick SE, Silverman JF. Fine needle aspiration biopsy of soft tissue sarcomas: utility and diagnostic challenges. *Adv Anat Pathol* 2004; 11(1):24–37.
 285. Kilpatrick SE, Ward WG, Chauvenet AR, et al. The role of fine needle aspiration biopsy in the initial diagnosis of pediatric bone and soft tissue tumors: an institutional experience. *Mod Pathol* 1998; 11:923–928.
 286. Abdul-Karim FW, Rader AE. Fine needle aspiration of soft-tissue lesions. *Clin Lab Med* 1998; 18(3):507–540, vi.
 287. Costa MJ, Campman SC, Davis RL, et al. Fine-needle aspiration cytology of sarcoma: retrospective review of diagnostic utility and specificity. *Diagn Cytopathol* 1996; 15(1):23–32.
 288. Kilpatrick SE. Histologic prognostication in soft tissue sarcomas: grading versus subtyping or both? A comprehensive review of the literature with proposed practical guidelines. *Ann Diagn Pathol* 1999; 3(1):48–61.
 289. Kilpatrick SE, Ward WG, Cappellari JO, et al. Fine-needle aspiration biopsy of soft tissue sarcomas: a cytomorphologic analysis with emphasis on histologic subtyping, grading, and therapeutic significance. *Am J Clin Pathol* 1999; 112(2):179–188.
 290. Jones C, Liu K, Hirschowitz S, Klipfel N, et al. Concordance of histopathologic and cytologic grading in musculoskeletal sarcomas: can grades obtained from analysis of the fine-needle aspirates serve as the basis for therapeutic decisions? *Cancer* 2002; 96(2):83–91.
 291. Geisinger KR, Abdul-Karim FW. Fine needle aspiration biopsies of soft tissue tumors. In: Weiss SW, Goldblum JR, eds. *Enzinger and Weiss’s Soft Tissue Tumors*. Saint Louis, MO: Mosby; 2001:147–188.
 292. Kilpatrick SE, Ward WG, Savage PD. Fine-needle aspiration biopsy of mesenchymal lesions: the value of clinicoradiologic correlation and the importance of histogenetic subtyping. *Am J Clin Pathol* 1997; 108(2):237.
 293. Kilpatrick SE, Renner J. Small round cell tumors of bone and soft tissues. In: Kilpatrick SE, ed. *Diagnostic Musculoskeletal Surgical Pathology with Clinicopathologic and Cytologic Correlations*. Philadelphia, PA: WB Saunders, 2004:37–70.
 294. Montgomery EA, Meis JM. Nodular fasciitis. Its morphologic spectrum and immunohistochemical profile. *Am J Surg Pathol* 1991; 15(10):942–948.
 295. Kapadia SB, Meis JM, Frisman DM, et al. Fetal rhabdomyoma of the head and neck: a clinicopathologic and immunophenotypic study of 24 cases. *Hum Pathol* 1993; 24(7):754–765.
 296. Afify AM, Liu J, Al-Khafaji BM. Cytologic artifacts and pitfalls of thyroid fine-needle aspiration using ThinPrep: a comparative retrospective review. *Cancer* 2001; 93(3):179–186.
 297. Akhtar M, Iqbal MA, Mourad W, et al. Fine-needle aspiration biopsy diagnosis of small round cell tumors of childhood: A comprehensive approach. *Diagn Cytopathol* 1999; 21(2):81–91.
 298. Kilpatrick SE, Renner J. Epithelioid/polygonal cell tumors. In: Kilpatrick SE, ed. *Diagnostic Musculoskeletal Surgical Pathology with Clinicopathologic and Cytologic Correlations*. Philadelphia, PA: WB Saunders, 2004:71–96.

299. Kilpatrick SE, Teot LA, Stanley MW, et al. Fine-needle aspiration biopsy of synovial sarcoma: a cytomorphologic analysis of primary, recurrent, and metastatic tumors. *Am J Clin Pathol* 1996; 106(6):769-775.
300. Fletcher CD, Gustafson P, Rydholm A, et al. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. *J Clin Oncol* 2001; 19(12):3045-3050.
301. Kilpatrick SE. Pleomorphic cell tumors of soft tissue and bone. In: Kilpatrick SE, ed. *Diagnostic Musculoskeletal Surgical Pathology*. Philadelphia, PA: WB Saunders, 2004:249-266.
302. Kilpatrick SE, Geisinger KR. Soft tissue sarcomas: the usefulness and limitations of fine-needle aspiration biopsy. *Am J Clin Pathol* 1998; 110(1):50-68.
303. Gonzalez-Campora R. Fine needle aspiration cytology of soft tissue tumors. *Acta Cytologica* 2000; 44(3):337-343.
304. Layfield LJ, Liu K, Dodge RK. Logistic regression analysis of myxoid sarcomas: a cytologic study. *Diagn Cytopathol* 1998; 19(5):355-360.
305. Kilpatrick SE, Inwards CY, Fletcher CD, et al. Myxoid chondrosarcoma (chordoid sarcoma) of bone: a report of two cases and review of the literature. *Cancer* 1997; 79(10):1903-1910.
306. Kilpatrick SE, Ward WG. Myxofibrosarcoma of soft tissues: cytomorphologic analysis of a series. *Diagn Cytopathol* 1999; 20(1):6-9.
307. Liao CT, Chang JT, Wang HM, et al. Survival in squamous cell carcinoma of the oral cavity: differences between pT4 N0 and other stage IVA categories. *Cancer* 2007; 110(3):564-571.
308. Bell RB, Kademani D, Homer L, et al. Tongue cancer: is there a difference in survival compared with other subsites in the oral cavity? *J Oral Maxillofac Surg* 2007; 65(2):229-236.
309. Mehrotra R, Gupta A, Singh M, et al. Application of cytology and molecular biology in diagnosing premalignant or malignant oral lesions. *Mol Cancer* 2006; 23:5-11.
310. Acha A, Ruesga MT, Rodriguez MJ, et al. Applications of the oral scraped (exfoliative) cytology in oral cancer and precancer. *Med Oral Patol Oral Cir Bucal* 2005; 10(2):95-102.
311. Ogden GR, Cowpe JG, Wight AJ. Oral exfoliative cytology: review of methods of assessment. *J Oral Pathol Med* 1997; 26(5):201-205.
312. Scher RL, Oostingh PE, Levine PA, et al. Role of fine needle aspiration in the diagnosis of lesions of the oral cavity, oropharynx, and nasopharynx. *Cancer* 1988; 62(12):2602-2606.
313. Frable MA, Frable WJ. Fine needle aspiration biopsy revisited. *Laryngoscope* 1982; 92(12):1414-1418.
314. Sandler HC. Errors of oral cytodiagnosis: Report of follow-up of 1,801 patients. *J Am Dent Assoc* 1966; 72(4):851-854.
315. Rovin S. An assessment of the negative oral cytologic diagnosis. *J Am Dent Assoc* 1967; 74(4):759-762.
316. Ljung BME, Larsson SG, Hanafee W. Computed tomography-guided aspiration cytologic examination in head and neck lesions. *Arch Otolaryngol* 1984; 110:604-607.
317. Statts OJ, Robinsn LH, Butterworth CJ. The effect of systemic therapy on nuclear size of oral epithelial cells in folate-related anemias. *Acta Cytol* 1969; 13:84.
318. Deery A. Oral cavity. In: Gray W, McKee GT, eds. *Diagnostic Cytopathology*. London, UK: Churchill Livingstone, 2003:325-332.
319. Silverman S Jr, Beumer J. Primary herpetic gingivostomatitis of adult onset. *Oral Surg Oral Med Oral Pathol* 1973; 36(4):496-503.
320. Medak H, Burlakow P, McGrew EA, et al. The cytology of vesicular conditions affecting the oral mucosa: pemphigus vulgaris. *Acta Cytol* 1970; 14(1):11-25.
321. Baurmash HD. Mucocoeles and ranulas. *J Oral Maxillofac Surg* 2003; 61(3):369-378.
322. Silverman SJ. Oral cavity. In: Bibbo M, ed. *Comprehensive Cytopathology*. Philadelphia, PA: WB Saunders, 1997:403-412.
323. Layfield L. *Fine needle aspiration of the head and neck*. Philadelphia, PA: WB Saunders, 1996.
324. Tani E, Ersoz C, Silfversward C, et al. Rhabdomyoma: primary diagnosis by fine needle aspiration (FNA) cytology and immunocytochemistry. *Cytopathology* 1995; 6(3):204-208.
325. McGregor DK, Krishnan B, Green L. Fine-needle aspiration of adult rhabdomyoma: a case report with review of the literature. *Diagn Cytopathol* 2003; 28(2):92-95.
326. Walker WP, Laszewski MJ. Recurrent multifocal adult rhabdomyoma diagnosed by fine needle aspiration cytology: report of a case and review of the literature. *Diagn Cytopathol* 1990; 6(5):354-358.
327. Pieterse AS, Mahar A, Orell S. Granular cell tumour: a pitfall in FNA cytology of breast lesions. *Pathology* 2004; 36(1):58-62.
328. Liu K, Madden JF, Olatidoye BA, et al. Features of benign granular cell tumor on fine needle aspiration. *Acta Cytol* 1999; 43(4):552-557.
329. Liu Z, Mira JL, Vu H. Diagnosis of malignant granular cell tumor by fine needle aspiration cytology. *Acta Cytol* 2001; 45(6):1011-1021.
330. Wicczorek TJ, Krane JF, Domanski HA, et al. Cytologic findings in granular cell tumors, with emphasis on the diagnosis of malignant granular cell tumor by fine-needle aspiration biopsy. *Cancer* 2001; 93(6):398-408.
331. Sun ZJ, Zhang L, Zhang WF, et al. Epithelioid hemangioendothelioma of the oral cavity. *Oral Dis* 2007; 13(2):244-250.
332. Pettinato G, Insabato L, De Chiara A, et al. Epithelioid hemangioendothelioma of soft tissue: fine needle aspiration cytology, histology, electron microscopy and immunohistochemistry of a case. *Acta Cytol* 1986; 30(2):194-200.
333. Tong GX, Hamele-Bena D, Borczuk A, et al. Fine needle aspiration biopsy of epithelioid hemangioendothelioma of the oral cavity: report of one case and review of literature. *Diagn Cytopathol* 2006; 34(3):218-223.
334. Mhoyan A, Weidner N, Shabaik A. Epithelioid hemangioendothelioma of the lung diagnosed by transesophageal endoscopic ultrasound-guided fine needle aspiration: a case report. *Acta Cytol* 2004; 48(4):555-559.
335. Cho NH, Lee KG, Jeong MG. Cytologic evaluation of primary malignant vascular tumors of the liver. One case each of angiosarcoma and epithelioid hemangioendothelioma. *Acta Cytol* 1997; 41(5):1468-1476.
336. Wakely PE, Frable WJ, Kneisl JS. Aspiration cytopathology of epithelioid angiosarcoma. *Cancer* 2000; 90(4):245-251.
337. Sun ZJ, Zhang L, Zhang WF, et al. Epithelioid hemangioma in the oral mucosa: a clinicopathological study of seven cases and review of the literature. *Oral Oncol* 2006; 42(5):441-447.
338. Baehner F, Sudilvsky D. Fine needle aspiration cytology of intraoral epithelioid hemangioma: a report of two cases. *Acta Cytol* 2003; 47(2):275-280.
339. Meyer I. Dermoid cysts (dermoids) of the floor of the mouth. *Oral Surg Oral Med Oral Pathol* 1955; 8(11):1149-1164.
340. Babuccu O, Fsiksacan-Ozen OI, Hosnuter M, et al. The place of fine needle aspiration in the preoperative diagnosis of the congenital sublingual teratoid cyst. *Diagn Cytopathol* 2003; 29(1):33-37.
341. Cramer H, Lampe H, Downing P. Dermoid cyst of the floor of the mouth diagnosed by fine needle aspiration cytology: a case report. *Acta Cytol* 1996; 40(2):319-326.

342. Acree T, Abreo F, Smith BR, et al. Diagnosis of dermoid cyst of the floor of the mouth by fine needle aspiration cytology: a case report. *Diagn Cytopathol* 1999; 20(2): 78–81.
343. Layfield L. *Cytopathology of the Head and Neck*. 1st ed. Chicago, IL: ASCP Press; 1997.
344. Kollur SM, El-Hag IA. Fine-needle aspiration cytology of metastatic nasopharyngeal carcinoma in cervical lymph nodes: comparison with metastatic squamous-cell carcinoma, and Hodgkin's and non-Hodgkin's lymphoma. *Diagn Cytopathol* 2003; 28(1):18–22.
345. Vesoulis Z. Metastatic laryngeal basaloid squamous cell carcinoma simulating primary small cell carcinoma of the lung on fine needle aspiration lung biopsy: a case report. *Acta Cytol* 1998; 42(3):783–787.
346. Gilcrease MZ, Guzman-Paz M. Fine-needle aspiration of basaloid squamous carcinoma: a case report with review of differential diagnostic considerations. *Diagn Cytopathol* 1998; 19(3):210–215.
347. Dejmek A, Lindholm K. Fine needle aspiration biopsy of cystic lesions of the head and neck, excluding thyroid. *Acta Cytol* 1990; 34(3):443–448.
348. Shahin A, Burroughs FH, Kirby JP, et al. Thyroglossal duct cyst: a cytopathologic study of 26 cases. *Diagn Cytopathol* 2005; 33(6):365–369.
349. Pisharodi LR. False-negative diagnosis in fine-needle aspirations of squamous-cell carcinoma of head and neck. *Diagn Cytopathol* 1997; 17(1):70–73.
350. Tanaka F, Wada H, Inni K, et al. Pulmonary metastasis of polymorphous low-grade adenocarcinoma of the minor salivary gland. *Thorac Cardiovasc Surg* 1995; 43(3): 178–180.
351. Gibbons D, Saboorian MH, Vuitch F, et al. Fine-needle aspiration findings in patients with polymorphous low grade adenocarcinoma of the salivary glands. *Cancer* 1999; 87(1):31–36.
352. Saenz-Santamaria J, Catalina-Fernandez I. Polymorphous low grade adenocarcinoma of the salivary gland: diagnosis by fine needle aspiration cytology. *Acta Cytol* 2004; 48(1): 52–56.
353. Watanabe K, Ono N, Saito K, et al. Fine needle aspiration cytology of polymorphous low-grade adenocarcinoma of the tongue. *Diagn Cytopathol* 1999; 20(3):167–169.
354. Mincione GP, Nesi G, Amorosi A. Polymorphous low-grade adenocarcinoma of the soft palate: fine needle aspiration (FNA) cytology. *Cytopathology* 1999; 10(1): 61–65.
355. Dee S, Masood S, Issacs JH Jr., et al. Cytomorphologic features of salivary duct carcinoma on the fine needle aspiration biopsy. A case report. *Acta Cytol* 1993; 37(4): 539–542.
356. Hales M, Bottles K, Miller T, et al. Diagnosis of Kaposi's sarcoma by fine-needle aspiration biopsy. *Am J Clin Pathol* 1987; 88(1):20–25.
357. Gamborino E, Carrilho C, Ferro J, et al. Fine-needle aspiration diagnosis of Kaposi's sarcoma in a developing country. *Diagn Cytopathol* 2000; 23(5):322–325.
358. Al-Rikabi AC, Haidar Z, Arif M, et al. Fine-needle aspiration cytology of primary Kaposi's sarcoma of lymph nodes in an immunocompetent man. *Diagn Cytopathol* 1998; 19(6):451–454.
359. Oliai BR, Sheth S, Burroughs FH, et al. "Parapharyngeal space" tumors: a cytopathological study of 24 cases on fine-needle aspiration. *Diagn Cytopathol* 2005; 32(1): 11–15.
360. Steirnerberg CM, Clark WD. Rhinoscleroma: A diagnostic challenge. *Laryngoscope* 1983; 93(7):866–870.
361. Zaharopoulos P, Wong JY. Cytologic diagnosis of rhinoscleroma. *Acta Cytol* 1984; 28(2):139–142.
362. Shabb N, Sneige N, Dekmezian RH. Myospherulosis fine needle aspiration cytologic findings in 19 cases. *Acta Cytol* 1991; 35(2):225–228.
363. Kyriakos M. Myospherulosis of the paranasal sinuses, nose and middle ear: a possible iatrogenic disease. *Am J Clin Pathol* 1977; 67(2):118–130.
364. Vuong PN. Acquired gluteal myospherulosis secondary to intramuscular injections of petrolatum-based hormones: a case report diagnosed by fine-needle aspiration cytology. *Diagn Cytopathol* 1988; 4(2):137–139.
365. Kumagami H. Testosterone and estradiol in juvenile nasopharyngeal angiofibroma tissue. *Acta Otolaryngol (Stockh)* 1991; 111:569–575.
366. Hosseini SM, Borghei P, Borghei SH, et al. Angiofibroma: an outcome review of conventional surgical approaches. *Eur Arch Otorhinolaryngol* 2005; 262(10):807–812.
367. Celik B, Erisen L, Saraydaroglu O, et al. Atypical angiofibromas: a report of four cases. *Int J Pediatr Otorhinolaryngol* 2005; 69(3):415–421.
368. Chhieng D, Cohen JM, Waisman J, et al. Fine-needle aspiration cytology of hemangiopericytoma: A report of five cases. *Cancer* 1999; 87(4):190–195.
369. Geisinger KR, Silverman JF, Cappellari JO, et al. Fine-needle aspiration cytology of malignant hemangiopericytomas with ultrastructural and flow cytometric analyses. *Arch Pathol Lab Med* 1990; 114(7):705–710.
370. Chan MKM, McGuire LJ, Lee JCK. Fine-needle aspiration cytodiagnosis of nasopharyngeal carcinoma in cervical lymph nodes. A study of 40 cases. *Acta Cytol* 1989; 33: 344–354.
371. Powers CN, Raval P, Schmidt WA. Fine needle aspiration cytology of metastatic lymphoepithelioma: a case report. *Acta Cytol* 1989; 33(2):254–258.
372. Ishikawa M, Kitayama J, Kaizaki S, et al. Diagnosis of nasopharyngeal carcinoma metastatic to mediastinal lymph nodes by endoscopic ultrasonography-guided fine-needle aspiration biopsy. *Acta Otolaryngol* 2005; 125(9):1014–1017.
373. Viguer JM, Jimenez-Heffernan JA, Lopez-Ferrer P, et al. Fine-needle aspiration cytology of metastatic nasopharyngeal carcinoma. *Diagn Cytopathol* 2005; 32(4):233–237.
374. Pacchioni D, Negro F, Valente G, et al. Epstein-Barr virus detection by in situ hybridization in fine-needle aspiration biopsies. *Diagn Mol Pathol* 1994; 3(2):100–104.
375. Macdonald MR, Freeman JL, Hui MF, et al. Role of Epstein-Barr virus in fine-needle aspirates of metastatic neck nodes in the diagnosis of nasopharyngeal carcinoma. *Head Neck* 1995; 17(6):487–493.
376. Kadish S, Goodman M, Wing CC. Olfactory neuroblastoma: a clinical analysis of 17 cases. *Cancer* 1976; 37(3):1571–1576.
377. Taxy JB, Bharani NK, Mills SE, et al. The spectrum of olfactory neural tumors: A light-microscopic, immunohistochemical and electron microscopic analysis. *Am J Surg Pathol* 1986; 10(10):687–695.
378. Chung J, Park ST, Jang J. Fine needle aspiration cytology of metastatic olfactory neuroblastoma: a case report. *Acta Cytol* 2002; 46(1):40–45.
379. Mahooti S, Wakely PE. Cytopathologic features of olfactory neuroblastoma. *Cancer* 2006; 108(2):86–92.
380. Logrono R, Futoran RM, Hartig G, et al. Olfactory neuroblastoma (esthesioneuroblastoma): appearance on fine-needle aspiration: report of a case. *Diagn Cytopathol* 1997; 17(3):205–208.
381. Ferris CA, Schnadig VJ, Quinn FB, et al. Olfactory neuroblastoma: cytodiagnostic features in a case with ultrastructural and immunohistochemical correlation. *Acta Cytol* 1988; 32(3):381–385.
382. Fagan MF, Rone R. Esthesioneuroblastoma: cytologic features with differential diagnostic considerations. *Diagn Cytopathol* 1985; 1(4):322–326.

383. Telen M, Wozniak Z, Rak J. Cytologic appearance of esthesioneuroblastoma in a fine needle aspirate. *Acta Cytol* 1988; 32:377–380.
384. Walker WP, Wittchow RJ, Bottles K, et al. Paranuclear blue inclusions in small cell undifferentiated carcinoma: a diagnostically useful finding demonstrated in fine-needle aspiration biopsy smears. *Diagn Cytopathol* 1994; 10(3):212–215.
385. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differential and differential diagnosis. *Adv Anat Pathol* 2005; 12(3):134–143.
386. Jeng Y-M, Sung M-T, Fang C-T, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal type undifferentiated carcinoma: two clinically, biologically and histopathologically distinct entities. *Am J Surg Pathol* 2002; 26:371–376.
387. Helsel JC, Bardales RH, Mukunyadzi P. Fine needle aspiration biopsy cytology of malignant neoplasms of the sinonasal tract. *Cancer* 2003; 99(2):105–112.
388. Cerilli LA, Holst VA, Brandwein MS, et al. Sinonasal undifferentiated carcinoma. Immunohistochemical profile and lack of EBV association. *Am J Surg Pathol* 2001; 25(2):156–163.
389. Loo CKC, Chin M, Farrell M, et al. Sinonasal neuroendocrine carcinoma: case report with FNA findings. *Pathology* 2006; 38:181–184.
390. McCluggage QWG, Napier SS, Primrose WJ. Sinonasal neuroendocrine carcinoma exhibiting amphicrine differentiation. *Histopathology* 1995; 27:79–82.
391. Perez-Ordóñez B, Caruana SM, Huvos AG, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *Hum Pathol* 1998; 29(8):826–832.
392. Rosenthal DI, Barker JL, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Cancer* 2004; 101(11):2567–2573.
393. Kleinsasser O, Schroeder HG. Adenocarcinoma of the inner nose after exposure to wood dust: morphological findings and relationships between histopathology and clinical behavior in 79 cases. *Arch Otorhinolaryngol* 1988; 245(1):1–15.
394. Rana RS, Dey P, Das A. Fine needle aspiration (FNA) cytology of extra-adrenal paragangliomas. *Cytopathology* 1997; 8(2):108–113.
395. Handa U, Bal A, Mohan H, et al. Parapharyngeal paraganglioma: diagnosis on fine-needle aspiration. *Am J Otolaryngol* 2005; 26(5):360–361.
396. Zaharopoulos P. Diagnostic challenges in the fine-needle aspiration diagnosis of carotid body paragangliomas: report of two cases. *Diagn Cytopathol* 2000; 23(3):202–207.
397. Das DK, Gupta AK, Chowdhury C, et al. Fine-needle aspiration diagnosis of carotid body tumor: report of a case and review of experience with cytologic features in four cases. *Diagn Cytopathol* 1997; 17(2):143–147.
398. Fleming MV, Oertel YC, Rodriguez ER, et al. Fine needle aspiration of six carotid body paragangliomas. *Diagn Cytopathol* 1993; 9(5):510–515.
399. Gonzalez-Caompora R, Ota-Salaverri C, Panea-Flores P, et al. Fine needle aspiration cytology of paraganglionic tumors. *Acta Cytol* 1988; 32:386–390.
400. Jacobs DM, Waisman J. Cervical paraganglioma with intranuclear vacuoles in a fine needle aspirate. *Acta Cytol* 1987; 31(1):29–32.
401. Vera-Alvarez J, Marigil-Gomez M, Abascal-Agorreta M, et al. Malignant retroperitoneal paraganglioma with intranuclear vacuoles in a fine needle aspirate: a case report. *Acta Cytol* 1993; 37(2):229–233.
402. Logrono R, Kurtycz DF, Wojtowycz M, et al. Fine needle aspiration cytology of fibrous dysplasia: a case report. *Acta Cytol* 1998; 42(5):1172–1176.
403. Li TJ, Sun LS, Luo HY. Odontogenic myxoma: a clinicopathologic study of 25 cases. *Arch Pathol Lab Med* 2006; 130(12):1799–1806.
404. Perez-Campos A, Perez-Rodriguez F, Azorin D, et al. Cytologic features of odontogenic myxoma. *Acta Cytol* 2004; 48(3):767–768.
405. Verma AK, Tandon R, Saxena S, et al. Aspiration cytology of maxillary myxoma. *Diagn Cytopathol* 1993; 9(2):202–204.
406. Gunhan O, Dogan N, Celasun B, et al. Fine needle aspiration cytology of oral cavity and jaw bone lesions: a report of 102 cases. *Acta Cytol* 1993; 37(2):135–141.
407. Ramzy I, Aufdemorte TB, Duncan DL. Diagnosis of radiolucent lesions of the jaw by fine needle aspiration biopsy. *Acta Cytol* 1985; 29(3):419–424.
408. Gupta K, Dey P, Goldsmith R, et al. Comparison of cytologic features of giant-cell tumor and giant cell tumor of tendon sheath. *Diagn Cytopathol* 2004; 30(1):14–18.
409. Cabrera RA, Almeida M, Mendonca ME, et al. Diagnostic pitfalls in fine-needle aspiration cytology of temporomandibular chondroblastoma: report of two cases. *Diagn Cytopathol* 2006; 34(6):424–429.
410. Kilpatrick SE, Pike EJ, Geisinger KR, et al. Chondroblastoma of bone: use of fine needle aspiration biopsy and potential diagnostic pitfalls. *Diagn Cytopathol* 1997; 16(1):65–71.
411. Tsaknis PJ, Nelson JF. The maxillary ameloblastoma: an analysis of 24 cases. *J Oral Surg* 1980; 38(5):336–342.
412. Akrish S, Buchner A, Shoshani Y, et al. Ameloblastic carcinoma: report of a new case, literature review, and comparison to ameloblastoma. *J Oral Maxillofac Surg* 2007; 65(4):777–783.
413. Radhika S, Nijhawan R, Das A, et al. Ameloblastoma of the mandible: diagnosis by fine-needle aspiration cytology. *Diagn Cytopathol* 1993; 9(3):310–313.
414. Stamatakis MD, Houston GD, Fowler CB, et al. Diagnosis of ameloblastoma of the maxilla by fine needle aspiration: a case report. *Acta Cytol* 1995; 39(4):818–820.
415. Parate SN, Anshu, Helwatkar SB, et al. Cytology of recurrent ameloblastoma with malignant change: a case report. *Acta Cytol* 1999; 43(6):1105–1107.
416. Matthew S, Rappaport K, Ali SZ, et al. Ameloblastoma: cytologic findings and literature review. *Acta Cytol* 1997; 41:955–960.
417. Philipsen HP, Reichart PA. Calcifying epithelial odontogenic tumor: biological profile based on 181 cases from the literature. *Oral Oncol* 2000; 36(1):17–26.
418. Shekarkhar MJ, Tabei SZ, Kumar PV, et al. Cytologic findings in calcifying epithelial odontogenic tumor: A case report. *Acta Cytol* 2005; 49(5):533–536.
419. Maiorano E, Renne G, Tradati N, et al. Cytological features of calcifying epithelial odontogenic tumor (Pindborg tumor) with abundant cementum-like material. *Virchows Arch* 2003; 442(2):107–110.
420. Maremonti P, Califano L, Mangone GM, et al. Intraosseous mucoepidermoid carcinoma: report of a long-term evolution case. *Oral Oncol* 2001; 37(1):110–113.
421. Zaharopoulos P. Primary intraosseous (central) salivary gland neoplasms in jaw bones: report of a mucoepidermoid carcinoma of the mandible diagnosed by fine needle aspiration cytology. *Diagn Cytopathol* 2004; 31(4):271–275.
422. Favia G, Maiorano E, Orsini G, et al. Central (intraosseous) adenoid cystic carcinoma of the mandible: report of a case with periapical involvement. *J Endod* 2000; 26(12):760–763.
423. Sato T, Indo H, Takasaki T, et al. A rare case of intraosseous polymorphous low-grade adenocarcinoma (PLGA) of the maxilla. *Dentomaxillofac Radiol* 2001; 30(3):184–187.

424. August M, Faquin WC, Ferraro NF, et al. Fine needle aspiration biopsy of intraosseous jaw lesions. *J Oral Maxillofac Surg* 1999; 57(11):1282-1286.
425. Curling M. The eye. In: Gray W, McKee GT, eds. *Diagnostic Cytopathology*. 2nd ed: Churchill Livingstone, 2003:977-994.
426. Makley TA Jr. Biopsy of intraocular lesions. *Am J Ophthalmol* 1967; 64:591-599.
427. Char DH. History of ocular oncology. *Ophthalmology* 1996; 103(suppl 8):S96-101.
428. Rosenthal DL, Mandell DB, Glasgow BJ. Eye. In: Bibbo M, ed. *Comprehensive Cytopathology*. Philadelphia, PA: WB Saunders, 1991:484-501.
429. Char DH, Kemnitz BA, Miller T. Intraocular biopsy. *Ophthalmol Clin North Am* 2005; 18(1):177-185.
430. Char DH. Tumors of the eye and ocular adnexa. Hamilton, Canada: BC Decker, 2001.
431. Machemer R, Parel JM, Buettner H. A new concept for vitreous surgery. Part 1. Instrumentation. *Am J Ophthalmol* 1972; 73(1):1-7.
432. Paerl R, Machemer R, Aumayr W. A new concept for vitreous surgery part 4: improvements in instrumentation and illumination. *Am J Ophthalmol* 1974; 77(1):6-12.
433. Green WR. Diagnostic cytopathology of ocular fluid specimens. *Ophthalmology* 1984; 91(6):726-749.
434. Engel HM, Green WR, Michels RG, et al. Diagnostic vitrectomy. *Retina* 1981; 1(2):121-149.
435. Engel HM, de la Cruz ZC, Jimenez-Abalahin LD, et al. Cytopreparatory techniques for eye fluid specimens obtained by vitrectomy. *Acta Cytol* 1982; 26:551-560.
436. Palexas GN, Green WR, Goldberg MF, et al. Diagnostic pars plana vitrectomy report of a 21-year retrospective study. *Trans Am Ophthalmol Soc* 1995; 93:281-308.
437. Gunduz K, Shields JA, Shields CL, et al. Cutaneous melanoma metastatic to the vitreous cavity. *Ophthalmology* 1998; 105(4):600-605.
438. Rastogi A, Jain S. Fine needle aspiration biopsy in orbital lesions. *Orbit* 2001; 20(1):11-23.
439. Augsburger JJ, Shields JA, Folberg R, et al. Fine needle aspiration biopsy in the diagnosis of intraocular cancer: cytologic-histologic correlations. *Ophthalmology* 1985; 92(1):39-49.
440. Czerniak B, Woyke S, Domagala W, et al. Fine needle aspiration cytology of intraocular malignant melanoma. *Acta Cytol* 1983; 2(27):157-165.
441. Scroggs MW, Johnston WW, Klintworth GK. Intraocular tumors: a cytopathologic study. *Acta Cytol* 1990; 34(3):401-408.
442. Palma O, Canali N, Scaroni P, et al. Fine needle aspiration biopsy: its use in the management of orbital and intraocular tumors. *Tumori* 1989; 75(6):589-593.
443. Eide N, Syrdalen P, Walaas L, et al. Fine needle aspiration biopsy in selecting treatment for inconclusive intraocular disease. *Acta Ophthalmol Scand* 1999; 77(4):448-452.
444. Glasgow BJ, Brown HH, Zargoza AM, et al. Quantitation of tumor seeding from fine needle aspiration of ocular melanomas. *Am J Ophthalmol* 1988; 105(5):538-546.
445. Zeppa P, Tranfa F, Errico M, et al. Fine needle aspiration (FNA) biopsy of orbital masses: a critical review of 51 cases. *Cytopathology* 1997; 8(6):366-372.
446. Karcioğlu ZA, Gordon RA, Karcioğlu GL. Tumor seeding in ocular fine needle aspiration biopsy. *Ophthalmology* 1985; 92(12):1763-1767.
447. Glasgow BJ, Layfield LJ. Fine needle aspiration biopsy of orbital and periorbital masses. *Diagn Cytopathol* 1991; 7(2):132-141.
448. Cangiarrella JF, Cajigas A, Savala E, et al. Fine needle aspiration cytology of orbital masses. *Acta Cytol* 1996; 40(6):1205-1211.
449. O'Hara BJ, Ehya H, Shields JA, et al. Fine needle aspiration biopsy in pediatric ophthalmic tumors and pseudotumors. *Acta Cytol* 1993; 37(2):125-130.
450. Shields JA, Shields CL, Ehya H, et al. Fine needle aspiration biopsy of suspected intraocular tumors: The 1992 Urwick Lecture. *Ophthalmology* 1993; 100(11):1677-1984.
451. Lobo A, Lightman S. Vitreous aspiration needle tap in the diagnosis of intraocular inflammation. *Ophthalmology* 2003; 110(3):595-599.
452. Tani E, Seregard S, Rupp G, et al. Fine needle aspiration cytology and immunocytochemistry of orbital masses. *Diagn Cytopathol* 2006; 34(1):1-5.
453. Gupta S, Sood B, Gulati M, et al. Orbital mass lesions: US-guided fine-needle aspiration biopsy. Experience in 37 patients. *Radiology* 1999; 213(2):568-572.
454. Czerniak B, Woyke S, Daniel B, et al. Diagnosis of orbital tumors by aspiration biopsy guided by computerized tomography. *Cancer* 1984; 54(11):2385-2389.
455. Zajdela A, de Maublanc MA, Schlienger P, et al. Cytologic diagnosis of orbital and periorbital palpable tumors using fine needle sampling without aspiration. *Diagn Cytopathol* 1986; 2(1):17-20.
456. Char DH, Kroll SM, Stoloff A, et al. Cytomorphometry of uveal melanoma: comparison of fine needle aspiration biopsy samples with histologic sections. *Anal Quant Cytol Histol* 1991; 13:293-299.
457. Faulkner-Jones BE, Foster WJ, Harbour JW, et al. Fine needle aspiration biopsy with adjunct immunohistochemistry in intraocular tumor management. *Acta Cytol* 2005; 49(3):297-308.
458. Zajdela A, Vielh P, Schlienger P, et al. Fine needle cytology of 292 palpable orbital and eyelid tumors. *Am J Clin Pathol* 1990; 93(1):100-104.
459. Kennerdell JS, Salmovits TL, Dekker A, et al. Orbital fine-needle aspiration biopsy. *Am J Ophthalmol* 1985; 99(5):547-551.
460. Arora R, Rewari R, Betharia SM. Fine needle aspiration cytology of orbital and adnexal masses. *Acta Cytol* 1992; 36(4):483-491.
461. Krohel GB, Tobin D, Chavis RM. Inaccuracy of orbital fine needle aspiration biopsy. *Ophthalmology* 1984; 91(suppl):83.
462. Cohen VM, Dinakaran S, Parsons MA, et al. Transvitreal fine needle aspiration biopsy: the influence of intraocular lesion size on diagnostic biopsy result. *Eye* 2001; 15(pt 2):143-147.
463. Augsburger JJ, Correa ZM, Schneider S, et al. Diagnostic transvitreal fine needle aspiration biopsy of small melanocytic choroidal tumors in nevus versus melanoma category. *Trans Am Ophthalmol Soc* 2002; 100:225-232.
464. Henderson JW, Neault RW. En bloc removal of intrinsic neoplasms of the lacrimal gland. *Trans Am Ophthalmol Soc* 1976; 74:133-147.
465. Stevenson KE, Hungerford J, Garner A. Local extraocular extension of retinoblastoma following intraocular surgery. *Br J Ophthalmol* 1989; 73(9):739-742.
466. Shields JA, Shields CL. Melanocytic tumors of the iris stroma. In: Shields JA, Shields CL, eds. *Intraocular Tumors: A Text and Atlas*. Philadelphia, PA: WB Saunders, 1992: 61-83.
467. Dey P, Radhika S, Rajwanshi A, et al. Fine needle aspiration biopsy of orbital and eyelid lesions. *Acta Cytol* 1993; 37(6):903-907.
468. Liu D. Complications of fine needle aspiration biopsy of the orbit. *Ophthalmology* 1985; 92(12):1768-1771.
469. Wilhelmus KR, Font RL, Lehmann RP, et al. Cytomegalovirus keratitis in acquired immunodeficiency syndrome. *Arch Ophthalmol* 1996; 114(7):869-872.

470. Mollan SP, Gao A, Lockwood A, et al. Postcataract endophthalmitis: incidence and microbial isolates in a United Kingdom region from 1996 through 2004. *J Cataract Refract Surg* 2007; 33(2):265–268.
471. Layfield LJ, Glasgow BJ, DuPuis MH. Fine needle aspiration of lymphoadenopathy of suspected infectious etiology. *Arch Pathol Lab Med* 1985; 109(9):810–812.
472. Froumis NA, Mondino BJ, Glasgow BJ. Acanthamoeba keratitis associated with fungal keratitis. *Am J Ophthalmol* 2001; 131(4):508–509.
473. Hunt KE, Glasgow BJ. Aspergillus endophthalmitis: an unrecognized endemic disease in orthotopic liver transplantation. *Ophthalmology* 1996; 103(5):757–767.
474. Mondino KM, Holland GN, Glasgow BJ. Retinal seeding from anterior segment coccidioidomycosis after vitrectomy. *Br J Ophthalmol* 2007; 91(6):837–838.
475. Kalogeropoulos CD, Malamou-Mitsi VD, Asproudis I, et al. The contribution of aqueous humor cytology in the differential diagnosis of anterior uvea inflammations. *Ocular Immunol and Inflamm* 2004; 12(3):215–225.
476. Mandell DB, Levy JJ, Rosenthal DL. Preparation and cytological evaluation of intraocular fluids. *Acta Cytol* 1987; 31(2):150–158.
477. Khatami M, Donnelly JJ, John T, et al. Vernal conjunctivitis: model studies in guinea pigs immunized topically with fluoresceinyl ovalbumin. *Arch Ophthalmol* 1984; 102(11):1683–1688.
478. Wilhelmus KR, Robinson NM, Tredici LL, et al. Conjunctival cytology of adult chlamydial conjunctivitis. *Arch Ophthalmol* 1986; 104(9):691–693.
479. Talley AR, Garcia-Ferrer F, Laycock KA, et al. Comparative diagnosis of neonatal chlamydial conjunctivitis by polymerase chain reaction and McCoy cell culture. *Am J Ophthalmol* 1994; 117(1):50–57.
480. Naib ZM. Cytology of ocular lesions. *Acta Cytol* 1972; 16(2):178–185.
481. Butrus SL, Abelson MB. Laboratory evaluation of ocular allergy. *Int Ophthalmol Clin*. 1988; 28:324–328.
482. Hochman M, Sugino IK, Lesko C, et al. Diagnosis of phacoanaphylactic endophthalmitis by fine needle aspiration biopsy. *Ophthalmic Surg Lasers* 1999; 30(2):152–154.
483. Hsuan JD, Selva D, McNab AA, et al. Idiopathic sclerosing orbital inflammation. *Arch Ophthalmol*. 2006; 124(9):1244–1250.
484. Sa HS, Ji JY, Suh YL, et al. Inflammatory myofibroblastic tumor of the orbit presenting as a subconjunctival mass. *Ophthalm Plast Reconstr Surg* 2005; 21(3):211–215.
485. Arora R, Rewari R, Betheria SM. Fine needle aspiration cytology of eyelid tumors. *Acta Cytol* 1990; 34(2):227–232.
486. Selsky EJ, Knox DL, Maumence AE, et al. Ocular involvement in Whipple's disease. *Retina* 1984; 4(2):103–106.
487. Johnson LN, Helper RS, Yee RD, et al. Sphenoid sinus mucocoele (anterior clinoid variant) mimicking diabetic ophthalmoplegia and retrobulbar neuritis. *Am J Ophthalmol* 1986; 102(1):111–115.
488. Gomez-Aracil V, Azua J, San Pedro C, et al. Fine needle aspiration cytologic findings in four cases of pilomatrixoma (calcifying epithelioma of Malherbe). *Acta Cytol* 1990; 34(6):842–846.
489. Unger P, Watson C, Phelps RG, et al. Fine needle aspiration cytology of pilomatrixoma (calcified epithelioma of Malherbe). Report of a case. *Acta Cytol* 1990; 34(6):847–850.
490. Sturgis CD, Silverman JF, Kennerdell JS, et al. Fine needle aspiration for the diagnosis of primary epithelial tumors of the lacrimal gland and ocular adnexa. *Diagn Cytopathol* 2001; 24(2):86–89.
491. Ni C. Primary lacrimal gland tumors: the pathologic classification of 272 cases. *Yen Ko Hsueh Pao* 1994; 10(4):201–220.
492. Shields CL, Shields JA, Eagle RC, et al. Clinicopathologic review of 142 cases of lacrimal gland lesions. *Ophthalmology* 1989; 96(4):431–435.
493. Glasgow BJ, Foos RY. *Ocular Cytopathology*. Boston, MA: Butterworth-Heinemann, 1993.
494. Cristallini EC, Bolis GB, Ottaviano P. Fine needle aspiration biopsy of orbital meningioma: report of a case. *Acta Cytol* 1994; 38:158–164.
495. Meyer E, Malberger E, Gdal-On M, et al. Fine needle aspiration of orbital lesions. *Ann Ophthalmol* 1983; 15(7):635–638.
496. Das DK, Das J, Bhatt NC, et al. Orbital lesions: diagnosis by fine needle aspiration cytology. *Acta Cytol* 1994; 38(2):158–164.
497. Malberger E, Tillinger R, Lichtig C. Diagnosis of basal cell carcinoma with aspiration cytology. *Acta Cytol* 1984; 28(3):301–304.
498. Johnson LN, Krohel GB, Yeon EB, et al. Sinus tumors invading the orbit. *Ophthalmology* 1984; 91(3):209–217.
499. Lee DA, Campbell RJ, Waller PR, et al. A clinicopathologic study of primary adenoid cystic carcinoma of the lacrimal gland. *Ophthalmology* 1985; 92(1):128–134.
500. Finger PT, Marin JP, Berson AM, et al. Choroidal metastasis from adenoid cystic carcinoma of the lung. *Am J Ophthalmol* 2003; 135(2):239–240.
501. Lloyd GA. Lacrimal gland tumors: the role of CT and conventional radiology. *Br J Radiol* 1981; 54(648):1034–1038.
502. Zurcher M, Hintschich CR, Garner A, et al. Sebaceous carcinoma of the eyelid: a clinicopathological study. *Br J Ophthalmol* 1998; 82(9):1049–1055.
503. Brownstein S, Codere F, Jackson WB. Masquerade syndrome. *Ophthalmology* 1980; 87(3):259–262.
504. Wright P, Collin JRO, Garner A. The masquerade syndrome. *Trans Ophthalmol Soc UK* 1981; 101:244–250.
505. Hood IC, Qizilbash AH, Salama SS, et al. Needle aspiration cytology of sebaceous carcinoma. *Acta Cytol* 1984; 28(3):305–312.
506. Das KK, Das J, Natarajan R, et al. Meibomian gland carcinoma initially identified by cytology. *Diagn Cytopathol* 1986; 12:154–156.
507. Jain P, Nanda A, Handa U, et al. FNA diagnosis of recurrent sebaceous carcinoma. *Diagn Cytopathol* 2006; 34(2):124–126.
508. Domagala W, Lubinski J, Lasota J, et al. Neuroendocrine (Merkel-cell) carcinoma of the skin. Cytology, intermediate filament typing and ultrastructure of tumor cell in fine needle aspirates. *Acta Cytol* 1987; 31(3):267–275.
509. Kawamoto E, Geisinger KR, Leonard DD, et al. The cytologic appearance of Merkel-cell carcinoma in fine needle aspirates. *Acta Cytol* 1984; 28:650.
510. Mellblom L, Akerman M, Carlen B. Aspiration cytology of neuroendocrine (Merkel-cell) carcinoma of the skin. Report of a case. *Acta Cytol* 1984; 28(3):297–300.
511. Garden JW, McManis JC. Congenital orbital-intracranial teratoma with subsequent malignancy: case report. *Br J Ophthalmol*. 1986; 70(2):111–113.
512. Samii M, Ramina R, Koch G, et al. Malignant teratoma of the optic nerve. Case report. *Neurosurgery* 1985; 16(5):696–700.
513. Mahesh L, Krishnakumar S, Subramanian N, et al. Malignant teratoma of the orbit: a clinicopathological study of a case. *Orbit* 2003; 22(4):305–309.
514. Char DH, Miller TR. Fine needle biopsy in retinoblastoma. *Am J Ophthalmol* 1984; 97(6):686–690.
515. Akhtar M, Ali MA, Sabbah R, et al. Aspiration cytology of retinoblastoma: light and electron microscopic correlations. *Diagn Cytopathol* 1988; 4(4):306–311.
516. Lussier C, Kljanienko J, Vielh P. Fine-needle aspiration of metastatic nonlymphomatous tumors of the major

- salivary glands: a clinicopathologic study of 40 cases cytologically diagnosed and histologically correlated. *Cancer* 2000; 90(6):350-356.
517. Shields JA, Shields CL, Parsons HM. Differential diagnosis of retinoblastoma: review. *Retina* 1991; 11(2):232-243.
 518. Karcioğlu ZA. Fine needle aspiration biopsy (FNAB) for retinoblastoma. *Retina* 2002; 22(6):707-710.
 519. Decaussin M, Boran MD, Salle M, et al. Cytological aspiration of intraocular retinoblastoma in an 11-year old boy. *Diagn Cytopathol* 1998; 19(3):190-193.
 520. Akhtar M, Ali MA, Sabbah R, et al. Fine needle aspiration biopsy diagnosis of round cell malignant tumors of childhood: a combined light and electromicroscopic approach. *Cancer* 1985; 55(8):1805-1817.
 521. Arora R, Betharia SM. Fine needle aspiration biopsy of pediatric orbital tumors. An immunocytochemical study. *Acta Cytol* 1994; 38(4):511-516.
 522. He W, Hasimoto H, Tsuneyoshi M, et al. A reassessment of histologic classifications and an immunochemical study of 88 retinoblastomas. A special reference to the advent of bipolar-like cells. *Cancer* 1992; 70(12):2901-2908.
 523. Takahashi T, Tamura S, Inoue M, et al. Retinoblastoma in a 26 year old adult. *Ophthalmology* 1983; 90(2):179-183.
 524. Shields CL, Shields JA, Gross NE, et al. Survey of 520 uveal metastases. *Ophthalmology* 1997; 104(8):1265-1276.
 525. Shields JA, Shields CL. Metastatic tumors to the intraocular structures. In: Shields JA, Shields CL, eds. *Intraocular Tumors: A Text and Atlas*. Philadelphia, PA: WB Saunders, 1992:207-238.
 526. Pollock SC, Awh CC, Dutton JJ. Cutaneous melanoma metastatic to the optic disc and vitreous. *Arch Ophthalmol* 1991; 109(10):1352-1354.
 527. Shields JA, Shields CL, Singh AD. Metastatic neoplasms in the optic disc. The 1999 Bjerrum Lecture: Part 2. *Arch Ophthalmol* 2000; 118:217-224.
 528. Reddy SC, Madhavan M, Mutum SS. Anterior uveal and episcleral metastases from carcinoma of the breast. *Ophthalmologica* 2000; 214(5):368-372.
 529. Heerema A, Sudilovsky D. Mucinous adenocarcinoma of the ovary metastatic to the eye: report of a case with diagnosis by fine needle aspiration biopsy. *Acta Cytol* 2001; 45(5):789-793.
 530. Singh RP, Tullis S, Hatton M, et al. Orbital metastasis from ovarian carcinoma in a patient with BRCA-2 mutation. *Ophthalm Plast Reconstr Surg* 2006; 22(4):298-299.
 531. Bouvier D, Raghuvver C. Aspiration cytology of metastatic chordoma to the orbit. *Am J Ophthalmol* 2001; 131(2):279-280.
 532. Otto RA, Templer JW, Renner G, et al. Secondary and metastatic tumors of the orbit. *Otolaryngol Head Neck Surg* 1987; 97(3):328-334.
 533. Shields JA, Shields CL, Ehya H. Lung cancer diagnosis by fine needle biopsy of the optic disk. *Retina* 2001; 21(6):665-666.
 534. Scolyer RA, Painter DM, Harper CG, et al. Hepatocellular carcinoma metastasizing to the orbit diagnosed by fine needle aspiration cytology. *Pathology* 1999; 31(4): 350-353.
 535. Srinivasan R, Krishnanand G. Cytologic diagnosis of metastatic hepatocellular carcinoma presenting as an orbital mass: a case report. *Acta Cytol* 2007; 51(1):83-85.
 536. Fan JT, Buettner H, Bartley GB, et al. Clinical features and treatment of seven patients with carcinoid tumor metastatic to the eye and orbit. *Am J Ophthalmol* 1995; 119(2):211-218.
 537. Freedman MI, Folk JC. Metastatic tumors to the eye and orbit: patients survival and clinical characteristics. *Arch ophthalmol* 1987; 105(9):1215-1219.
 538. Ritland JS, Eide N, Walaas L, et al. Fine needle aspiration biopsy diagnosis of uveal metastasis from a follicular thyroid carcinoma. *Acta Ophthalm Scand* 1999; 77(5):594-596.
 539. Irving RM, Parikh A, Coumbe A, et al. Melanotic neuroectodermal tumor of infancy. *J Laryngol Otol* 1993; 107(11):1045-1048.
 540. Judd PJ, Pedod D, Harrop K, et al. Melanotic neuroectodermal tumor of infancy. *Oral Surg Oral Med Oral Pathol* 1990; 69:723-726.
 541. Mirich DR, Blaser SI, Harwood-Nash DC. Melanotic neuroectodermal tumor of infancy: clinical, radiologic, and pathologic findings in five cases. *Am J Neuroradiol* 1991; 12(4):689-697.
 542. Borello DE, Gorlin RJ. Melanotic neuroectodermal tumor of infancy: a neoplasm of neural crest origin. Report of a case associated with a high urinary excretion of vanilmandelic acid. *Cancer* 1966; 19:196-206.
 543. Galera-Ruiz H, Gomez-Angel D, Vazquez-Ramirez FJ, et al. Fine needle aspiration in the preoperative diagnosis of melanotic neuroectodermal tumor of infancy. *J Laryngol and Otol* 1999; 113(6):581-584.
 544. El-Harazi SM, Kellaway J, Font RL. Melanocytoma of the ciliary body diagnosed by fine-needle aspiration biopsy. *Diagn Cytopathol* 2000; 22(6):394-397.
 545. Joffe I, Shields J, Osher R, et al. Clinical and follow-up studies of melanocytomas of the optic disc. *Ophthalmology* 1979; 86:1067-1078.
 546. Juarez CP, Tso MO. An ultrastructural study of melanocytomas (magnocellular nevi) of the optic disk and uvea. *Am J Ophthalmol* 1980; 90(1):48-62.
 547. Char DH, Miller TR, Crawford JB. Cytopathologic diagnosis of benign lesions simulating choroidal melanomas. *Am J Ophthalmol* 1991; 112(1):70-75.
 548. Shields JA, Shields CL, De Potter P, et al. Diagnosis and treatment of uveal melanoma. *Semin Oncol* 1996; 23(6):763-767.
 549. Paridaens ADA, McCartney ACE, Curling OM, et al. Impression cytology of conjunctival melanosis and melanoma. *Br J Ophthalmol* 1992; 76:198-201.
 550. Woyke S, Domagala W, Czerniak B, et al. Fine needle aspiration cytology of malignant melanoma of the skin. *Acta Cytol* 1980; 24:529-538.
 551. Martinez F, Merenda G, Bedrossian CW. Lipid-rich metastatic melanoma: diagnosis by a multimodal approach to aspiration biopsy cytology. *Diagn Cytopathol* 1990; 6:427-433.
 552. Tseng S-H, Chen Y-T, Huang F-C, et al. Seborrhic keratosis of conjunctiva simulating a malignant melanoma: an immunocytochemical study with impression cytology. *Ophthalmology* 1999; 190:1516-1520.

Uses, Abuses, and Pitfalls of Frozen-Section Diagnoses of Diseases of the Head and Neck

Mario A. Luna

*Department of Pathology, The University of Texas, M.D. Anderson Cancer Center,
Houston, Texas, U.S.A.*

I. INTRODUCTION

The frozen-section tissue examination, performed during surgery while the patient is still under anesthesia, was introduced 100 years ago, and the technique is accepted as an integral part of the proper surgical treatment of a patient (1,2). Entire generations of pathologists and surgeons have become familiar with the method and its benefits to them and their patients. Although frozen sections may be requested by surgeons for several specific reasons, all are based on their desire to obtain accurate diagnostic information, from which they will decide on the immediate surgical procedure.

Frozen-section diagnosis should be considered a cooperative effort between physicians, because the surgical pathologist's report carries the same weight as that of any other consulting physician. It is imperative that a sound dialogue be established between the surgeon and pathologist over the need for, limitations of, and consequences of the frozen-section diagnosis; however, the actual decision of whether or not to prepare a frozen section is up to the pathologist, rather than the surgeon.

II. HANDLING OF THE TISSUE SAMPLE

Fragments of tissue obtained for frozen sections should be sent to the pathologist in the unfixed state. Immersion in formalin, even for a brief time, interferes with adherence of the sections to the glass slide, makes the technique more difficult, and may inhibit the performance of special studies, such as cultures and immunofluorescence. To avoid desiccation, the specimen may be sent to the pathology laboratory, wrapped in a piece of gauze moistened with saline solution.

III. TECHNIQUE FOR PREPARING A FROZEN SECTION

The technique of frozen-section preparation is not difficult, although the sections must be thin and clearly stained, and the study should be completed

within a short time. The use of the cold chamber cryostat, introduced into surgical pathology in the late 1950s by Ibanez et al. (3), has eliminated most of the technical shortcomings of the procedure. In most instances, the quality of the preparations is equal to or only slightly less perfect than that of permanent sections subjected to paraffin embedding.

Several methods and a variety of microtomes are currently available for the preparation of frozen sections. Within 15 minutes, the newer cryostats can provide a satisfactory section stained with hematoxylin and eosin (H&E). At the M. D. Anderson Hospital the procedure is as follows: The biopsy specimen removed at time of surgery is transported to the pathology laboratory by surgical personnel; because the frozen-section laboratory is adjacent to the operating rooms, the transportation takes little time. The gross specimen is examined by a staff pathologist and a pathology resident, and a representative portion is selected for cryostat sectioning. All tissue sections are prepared by a technologist. The tissue is embedded on a metal chuck with the use of a commercial preparation (OCT, optimal cutting temperature compound, manufactured by Laboratory Technical Instruments Company, Westmont, Illinois, U.S.). The compound is sectioned with the tissue, but disappears in the staining process.

For freezing, the metal chuck is placed in an insulated stainless steel box containing aluminum racks, around which dry ice is packed into the box. The temperature of the box is -66°C or less. Into the top of the racks, cylindrical cavities have been drilled for the tissue holders; these cavities are filled with 95% ethyl alcohol. The metal chuck containing the specimen of tissue is inserted into one of the cylindrical cavities of the rack. From 15 to 20 seconds are required for freezing a block of tissue $15 \times 15 \times 3$ mm in diameter. When frozen, the tissue, with the holder attached, is placed on the microtome inside the cold chamber and sections are cut at 6 to $8/\mu\text{m}$ for fixation. The slides, with the tissue attached, are next immersed for a few seconds in a solution composed of equal parts of ether and absolute methyl alcohol and then stained with H&E. Stained sections are mounted and

retained for permanent reference. The time required for preparation and microscopic interpretation averages 10 minutes. The pathologic diagnosis is relayed directly to the surgeon by an intercommunicating system. The exact verbal report is recorded by the pathologist on a specially designed "Frozen Section Diagnosis Form," which becomes a permanent part of the pathology record of the patient. A duplicate of the diagnosis form is retained in the laboratory.

A much faster technique has been used at the Mayo Clinic for many years, with excellent results (4). The difference is that the tissue slides are stained with toluidine blue instead of using the conventional H&E stain (5). The only inconvenience is that tissue stained with toluidine blue will fade with time and cannot be retained as permanent reference.

Dehner and Rosai (6) have emphasized the importance of keeping a written record of the frozen-section diagnosis exactly as it was verbally rendered. They have given the following reasons for this precaution: (i) It provides a permanent record for medical and legal purposes, (ii) it protects the pathologist and surgeon from possible misunderstanding at the time of verbal communication, and (iii) it provides a retrievable format for periodic evaluation of the procedure.

IV. ACCURACY

In reviewing publications evaluating the accuracy of frozen-section diagnosis in head and neck surgery, one is impressed by the generally high degree of accuracy obtained. The figures quoted have often included deferred diagnoses. When these are excluded, the number of accurate diagnoses has varied from 97% to 99%. This figure compares favorably with the 0.7% to 2.5% rate of error reported previously in general surgery (4,6-16). Dehner and Rosai (6) quoted an accuracy rate of 96% on 1187 individual nondeferred frozen sections. This is identical with the data of Remsen et al. (11) and Bauer (12), which dealt exclusively with frozen tissues from the head and neck. Also, of interest is the pronounced difference between the incidence of false-positive and false-negative diagnoses. The percentage of false-negatives is quite low, although still three times that of false-positives. There is no doubt that the attitude of the pathologist is, as a rule, one of extreme conservatism in handling frozen-section material. As a consequence, confronted with the situation in which the problem of neoplasia must be resolved, we are three times as likely to err on the side of conservatism.

Gandour-Edwards et al. (13) analyzed the accuracy of frozen-section diagnosis in head and neck surgery in relation to the reason for the intraoperative request. Their accuracy rate in 1947 specimens for evaluation of adequacy of surgical margins was 98.3%. The accuracy rate for diagnosis of an unknown process in 258 specimens was 96.6%, and no discrepancies occurred in the five requests for tissue identification. Analysis of accuracy of consultation by anatomic region of the head and neck revealed certain

differences. Remsen et al. (11) found an accuracy rate of 100% on the submandibular gland, nose, and paranasal sinuses, followed by the thyroid gland (99.2%), neck (97%), parotid gland (95.4%), skin (94.3%), and larynx (93.2%). Areas in which frozen-section diagnosis was least accurate included the nasopharynx (87.5%) and the oropharynx (91.3%).

Factors involved in improving the reliability of frozen sections are (i) preparations of high quality with the use of the cryostat, (ii) experience of the pathologist in performing frozen-section diagnoses, (iii) familiarity of the pathologist with the clinical history of the patient, (iv) direct communication with the surgeon, (v) availability of a qualified histology technologist, (vi) readily available consultation with staff pathologists, (vii) close cooperation between an experienced surgeon interested in pathology and a pathologist dedicated to patient care, (viii) continual retrospective critical analysis of performance, and (ix) examination of selected cases and periodic discussion of frozen sections with the surgical team.

V. ERRORS

Four types of errors are possible in frozen-section diagnosis: sampling, interpretive, communicative, and technical (16). Although improper surgical or pathologic sampling errors are unavoidable, the number may be reduced by an even more cautious gross examination or by cutting additional sections of tissue from different levels of the block submitted for frozen-section diagnosis. In my experience, the latter practice is especially useful in studies of cervical lymph nodes in metastatic melanoma and thyroid carcinoma. Gross-sampling errors by pathologists are not unusual in neoplasms of the salivary and thyroid glands.

Interpretive errors are those made when the pathologist fails to recognize a lesion that is actually present in the frozen sections. In tissues from the head and neck, this error is not uncommon in the interpretation of sites of a previous laryngeal biopsy (13), in irradiated tissues (16), and in unsuspected, unusual lesions. In the first and second cases, it is helpful if the pathologist has knowledge of the clinical history of the patient and has reviewed the previously removed histologic material. In the last instance, given clinical information and adequate tissue, the pathologist may still have difficulty in arriving at a correct diagnosis. Only the experience of the surgical pathologist can reduce interpretive errors.

Lack of identification of the exact source of the tissue specimen submitted for frozen-section diagnosis is the communicative error most often committed by the clinician. This neglect is especially frustrating in the histopathologic evaluation of lymph nodes of the neck if the typical surgical pathology request form contains nothing more than the information "cervical node." Such a problem can be solved only through the exchange of information between the surgeon and the pathologist.

Technical factors, for example, slides of poor quality, lead to interpretive errors by the pathologist.

This, however, should not be accepted as the sole cause of error. The pathologist is the “captain of the ship” in the frozen-section laboratory. We agree with Saltzstein and Nahum that “the surgical pathologist should be aware that he is having problems and either correct them if at all possible or, if he is unable to correct them, report the situation to the surgeon” (16).

VI. INDICATIONS AND CONTRAINDICATIONS

A. Indications

The indications for the frozen-section examination, which have been discussed at length by many authors (4,6–16) are, briefly, as follows:

1. As an initial study, to obtain a histologic diagnosis when a definitive therapeutic procedure is to be carried out immediately. If, however, the treatment would be the same, regardless of the nature of the lesion or of other information gained, there is no justification for a frozen section.
2. To assess the adequacy of the surgical excision by a check of the margins of resection. Frozen-section examination of the margins of neoplasms of the head and neck is a common practice.
3. To preliminarily assess the nature of the planned procedure, as determined by the extent and distribution of the tissue involved by tumor. This is especially common in laryngeal surgery in which the decision is between partial and total laryngectomy.
4. To identify or diagnose any abnormality of tissue observed during surgery that gives rise to a question in the surgeon’s mind.
5. To ascertain whether a biopsy is satisfactory for diagnostic purposes, thus eliminating the need for additional multiple biopsies, even though further surgery is not contemplated at the time. This point is not infrequently presented when lymphoma is suspected clinically and a cervical lymph node or tonsillar biopsy is performed. In such cases, one-half of the specimen should be used for frozen section, while the other half is fixed for paraffin sectioning to eliminate the development of artifacts incident to freezing.
6. To determine if a lesion requires immediate or special handling. For example, tissue for electron microscopy and immunofluorescence requires special treatment for optimal results. By knowing that a lesion is inflammatory, one will be able to obtain adequate bacteriologic or viral cultures.
7. To use the frozen-section technique when necessary on biopsies taken from outpatients. This procedure allows triage of a large number of patients with lesions of the upper respiratory and digestive tracts and rapid scheduling and treatment when necessary.

The reasons for requesting an intraoperative consultation in head and neck surgery have been analyzed by Gandour-Edwards et al. (13). In their material of 2210 frozen sections from 258 patients, 88.1% (1947) of sections were requested for evaluation

of adequacy of surgical margins, 11.7% (25) for diagnosis, and only 0.2% (5) for tissue identification.

B. Contraindications

The contraindications for and misuses of frozen section are as follows:

1. When the frozen-section diagnosis carries no immediate decision, for example, academic curiosity, drama, or gamesmanship.
2. If tissue is heavily calcified or ossified.
3. If the tissue specimen is unique and small.
4. For lesions that, even under optimum conditions, require extensive study because of their complexity. These include the lymphoreticular disorders, small superficial melanocytic lesions, and some granulomatous diseases.

VII. INTRAOPERATIVE CYTOLOGY

The use of imprint and smear cytology is a useful adjunct to the frozen section, with proved acceptable accuracy rate (17–20). The reports that have compared intraoperative cytologic techniques with frozen sections have noted similar accuracy rates. However, when both techniques are combined, this figure increases to almost 100% (20). Cytologic techniques are particularly useful when sampling lymph nodes that are suggestive of either lymphoma or metastatic disease, parathyroid tumors, salivary gland tumors, or thyroid lesions (21–23).

The greatest advantage of cytologic examination is that minimal tissue is needed for examination; therefore, diagnosis of very small lesions is facilitated, and tissue is saved for permanent sections and special studies. Certain tissues that often cannot be adequately assessed by frozen section for technical reasons (e.g., bone, fat, or necrotic tissue) may be also appropriate for intraoperative cytologic diagnosis.

There are several situations in which an intraoperative cytologic study is generally not as useful as frozen-section examination. These include the evaluation of resection margins, the presence or absence of stromal invasion, or the depth of invasion of a malignant neoplasm (17–23).

VIII. REGIONAL APPLICATIONS OF FROZEN-SECTION DIAGNOSIS

A. Surgical Margins

Successful local control of a malignant tumor depends on eradication not only of the gross disease but also of its microscopic or subclinical extension (24–27). Usually an experienced surgeon is able to resect the palpable or visible tumor with a fringe of normal tissue and feel confident of its complete removal in 67% of the cases (24). Occasionally, however, to the chagrin of the surgeon, the pathology report, completed several days postoperatively, indicates the presence of microscopic cancer at the resected margins. To avoid this dilemma, the experienced surgeon, with the

aid of a pathologist competent in frozen-section evaluations, can determine the extent of the resected tumor, pinpoint areas of any microscopic cut-through, and usually tailor the surgical procedure to completely eradicate the local disease. The reliability and usefulness of frozen sections to assess surgical margins is well documented with an accuracy rate of 99% (28). However, frozen sections do have limitations and frozen sections are not always helpful in preventing final positive margins (28). To be assured of adequate margins when assessing a resected malignant tumor, the pathologist must be familiar with the patient's anatomy in the area of the operation, must possess an intimate knowledge of the clinical behavior of the various types of tumor with which the surgeon deals, and must develop a close working relation with the surgeon during frozen-sections examination (29). Measurements of margins on formalin-fixed specimens are inferior to in situ, frozen-section samples because of postremoval and postfixation shrinkage. Formalin-fixation, according to some studies, produces an overall mean shrinkage of 2.7%, and dehydration, clearing, and paraffin embedding account for 12.5%. Other studies, however, indicate that tissue processing may result in a reduction or shrinkage as high as 46% from the planned surgical margin before resection to the assessed measurement of microscopic clearance in the pathology laboratory (29).

The concept of adequate margins varies from surgeon to surgeon and there is no uniform criteria accepted to define a clear surgical margin among practicing head and neck surgeons (30,31). The concept of adequate surgical margins is influenced by the size and type of the neoplasm, its anatomic site, and the type of operation (conservative, palliative, or radical) required. A surgical margin that is considered to be adequate for a well-differentiated squamous carcinoma is of a different order from that indicated for an adenoid cystic carcinoma or melanoma (29,32). The finding of a significant relationship between involved margins and pT stage grouping is not surprising (32). It is logical that large tumors are more difficult to resect, given the anatomical restraints that operate in many sites of the head and neck. The surgical margins vary according to the anatomical region; margins from carcinoma of the glottis cannot be compared with those carcinomas of the oral cavity and oropharynx. In a study by Bauer et al. (33), 39 of 111 patients treated by hemilaryngectomy had positive margins, none of the patients received any further therapy, and in 5 to 12 years follow-up local recurrences developed in only 7 of 39 (18%). In contrast, the reported local recurrence rate in patients with carcinoma of the oral cavity, oropharynx, and hypopharynx whose pathologic specimens exhibited positive margins is 71% (25,26). Also, the presence of dysplasia, carcinoma in situ, and invasive carcinoma at the surgical margins cannot be placed in the same category. In the study of Loree and Strong (26), the five-year survival rate was drastically different (94% of patients with dysplasia, 71% of those with in situ carcinoma, and 43% of those with invasive carcinoma at the



Figure 1 Preparation of circumferential margins taken by the pathologist for frozen-section examination.

margin). From the pathologist's point of view, in situ carcinoma, severe dysplasia, and microinvasive carcinoma have equal biologic significance (29).

The surgical margins for frozen section may be removed by two methods (24–26). In the first, depending on the size of the tissue and the nature of the tumor, the pathologist may take full-thickness samples or, alternatively, circumferential margins in addition to the base of the specimen (Fig. 1). In the second method, the surgeon removes the surgical margins directly from the patient and submits them for frozen-section examination (Fig. 2). If positive, provides sequential margins until the new margin is free of neoplasm on frozen-section examination. This is the method used by most of the head and neck surgeons at our institution since 2005.

The usual practice at the M. D. Anderson Hospital, when the pathologists take the sections for frozen



Figure 2 Surgical resection of cancer. Margins of resection taken by the surgeon directly from the patient and submitted for frozen-section examination.

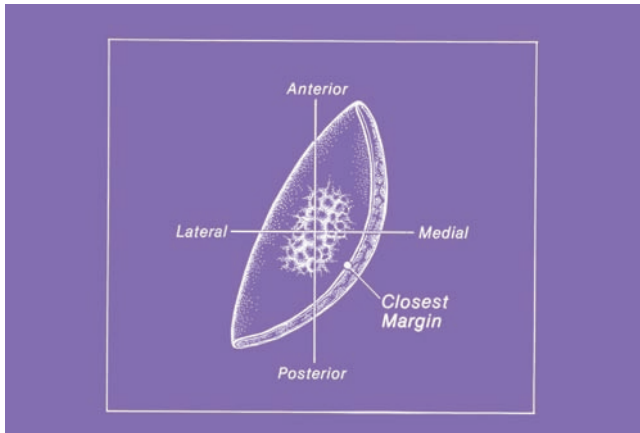


Figure 3 Processing of surgical specimen. Sections are taken from the different margins of resection as well as from the closest margins.

section, is as follows: the surgeon personally delivers the resected tumor to the pathologist, orients the specimen for him, and observes while the margins are excised and examined microscopically (22,27). If the margin is inadequate at any point, or if the tumor is grossly very close, further marginal tissue is excised and submitted for additional frozen-section evaluation until a clear margin is confirmed or the surgical procedure is terminated. However, it has to be recognized that in those cases when the margin was initially positive on frozen section, the assumption that the final margins are negative may not be an accurate assumption, because the well-known problems of relocating the site from which the frozen section was positive (27,34).

The frozen-section technique used to evaluate the margins of the resected lesion consists of the following: (i) The closest border of the resected lesion is stained with india ink to determine its position as medial-lateral, superior-inferior, or anterior-posterior (Fig. 3). (ii) Serial full-thickness sections are made, the lesion being sliced like a loaf of bread when possible (Fig. 4); if this is not feasible, sections are taken from all of the edges of the lesion, as well as of the base. As the histologic frozen sections for microscopic evaluation exhibit the full thickness, these should include the mucosal surface as well as base of excision and not have tissue defects (Fig. 5).

For the mandibular margin of resection, a touch imprint cytologic preparation or cryostat sections of curetted samples of the cancellous bone have served as specimens with varying degrees of success and acceptance. Forest et al. (35), with a 1-cm curettage specimen and frozen section, were able to correctly predict adequacy of mandibular resection in 32 of 33 margins. Oxford and Ducic (36) have developed a simple technique that allowed frozen-section examination of cortical bony margins in 38 patients; the method has a sensitivity of 89% and a specificity of 100%. Malignancies diagnosed on frozen cortical bone



Figure 4 Ideal preparation for study of surgical margins for frozen section.

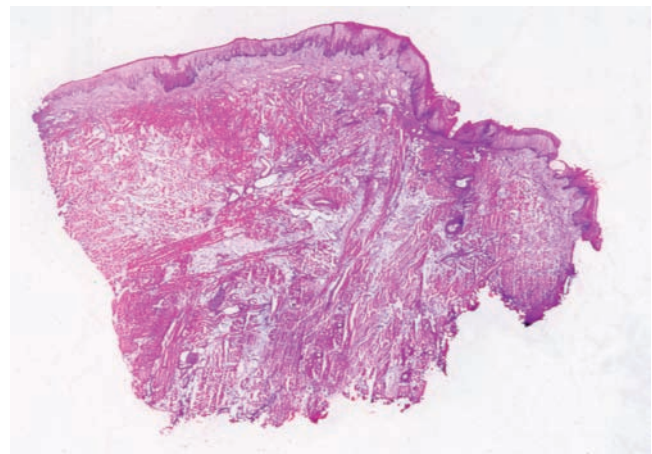


Figure 5 Histologic frozen-section slide of surgical margin. Sections should include full thickness from surface to base of excision without tissue defects (cryostat-prepared section, H&E stained). *Abbreviation:* H&E, hematoxylin and eosin.

specimens included 15 squamous cell carcinomas, 3 mucoepidermoid carcinomas, and 3 sarcomas (36).

For “adequate” surgical margins, the following observations are pertinent:

1. No standard guidelines on evaluating surgical margins intraoperatively have been established.
2. No uniform criteria to define a clear surgical margin exist among practicing head and neck surgeons.
3. Frozen-section examination is the ideal method to assess distance between tumor and surgical margins because of postremoval and postfixation shrinkage.
4. In spite of the lack of universally defined clear margins, there is little doubt that gross residual tumor will yield local persistence and nearly always an increased mortality.

5. A significantly lower incidence of local recurrence is reported in patients with primary cancers of the glottic larynx who had positive surgical margins than in patients who had primary tumors of the oral cavity, oropharynx, or hypopharynx with positive surgical margins.
6. For T1, T2, and T3 carcinomas of the oral cavity, oropharynx, and hypopharynx, a 1-cm margin is advisable. The margin of safety is reduced to 0.5 cm for laryngeal carcinoma, which is amenable to conservative surgery. Laryngeal specimens with margins of 2 mm or less carry a five-year survival rate, equal to that of patients with neoplasms at the resected margins. Patients whose resected larynges have a margin of clearance greater than 2 mm do almost as well as those with a widely clear margin.
7. These issues could be addressed in a multicentric prospective trial.

B. Peripheral Nerves

The frozen-section technique has been invaluable for studying the spread of tumor through the peripheral nerves, especially those in the head and neck. In these locations the invasion and extension along the branches of the cranial nerves is of particular significance (37–39). Once a branch is invaded, the disease is certain to extend to the dura mater and brain (37,40). To prevent this, the involved segment of nerve must be removed as a principal part of the surgical procedure and studied by frozen section. The nerves most frequently involved are the greater palatine nerve, by tumors of the palate; the maxillary nerve, by tumors of the maxilla; the lingual nerve, by tumors of the tongue, floor of mouth, and submaxillary gland; the mental nerve by cancer of the lip (Fig. 6); and the facial nerve, and branches of the auriculotemporal nerve by tumors of the parotid gland (37–39). Any malignant tumor of the head and neck can invade the cranial nerves, but the more common are adenoid cystic carcinoma (39), skin carcinoma of the face (40), facial melanoma (41), and squamous cell carcinoma of the lip, sinuses, and tongue (37,38).

For frozen-section examination of a nerve, the procedure is as follows: A platform of OCT compound

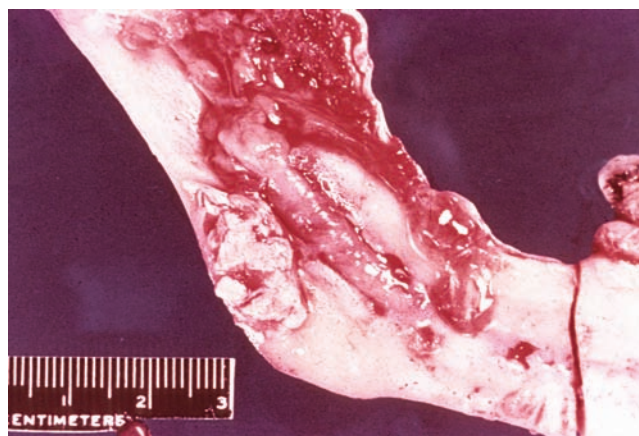


Figure 6 Gross specimen showing mental nerve invaded by squamous carcinoma of the lip.

is made for mounting the nerve on the tissue holder and the section is made in the longitudinal axis. The proximal end of the nerve should be cut transversely for study of the entire circumference (Fig. 7).

C. Lymph Nodes

Frozen sections of enlarged cervical lymph nodes permit a full range of pathologic interpretation, among other things, primary lymphoma, metastatic carcinoma, granuloma, or nonspecific reactive hyperplasia. A tumor diagnosed preoperatively as an enlarged cervical lymph node may prove, on frozen section, to be an unsuspected neoplasm or cyst. Paragangliomas, schwannoma, Warthin's tumor, or cyst of the branchial cleft, all have been responsible, on occasion, for a preoperative diagnosis of "indeterminate cervical adenopathy" (see chaps. 16 and 17).

Usually, the diagnosis of carcinoma within a lymph node is easy; lymph nodes from patients with known cancer are often submitted. Keratinizing squamous carcinoma, papillary carcinoma, and mucinous carcinoma are recognized without any problem. If

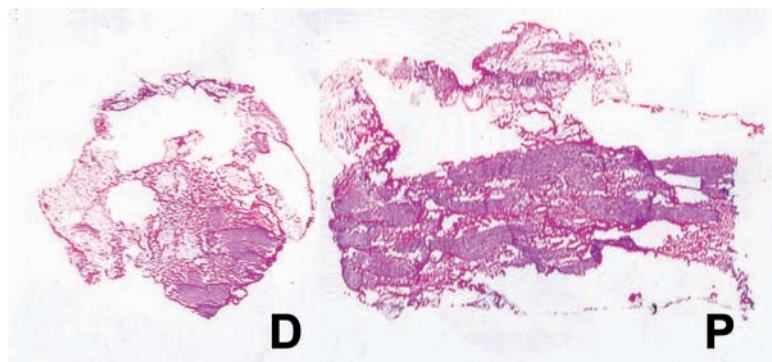


Figure 7 Routine preparation of peripheral nerve. Note the transverse section of the proximal margin (P). Distal margin (D) (cryostat-prepared section, H&E stained). *Abbreviation:* H&E, hematoxylin and eosin.

the initial section is negative, step sections of the block should be studied to detect any small foci of carcinoma in the capsular lymphatics and subcapsular sinusoids.

Lymph nodes are the specimens most frequently subjected to a deferred diagnosis (6), especially when the possibility of lymphoma is entertained. The problems associated with the diagnosis of lymphoma and in the classification of lymphomatous involvement of lymph nodes are well recognized; we are often reluctant to attempt such evaluation on frozen section. The distinction between lymphoma and diffuse or follicular hyperplasia may be extremely difficult, and for this, half of the lymph node should be used for frozen section, the other half being fixed for paraffin sectioning to eliminate the formation of artifacts incident to freezing. In these circumstances, the frozen-section examination is made to confirm the presence or absence of disease and to ascertain if the tissue is adequate for diagnosis.

Frozen-section analysis of the sentinel lymph node (SLN) in patients with clinically N0 squamous cell carcinoma of the oral cavity and oropharynx have proved to be of great help in their management to decide if a neck dissection was necessary. Tschopp et al. (42) analyzed 82 SLN by frozen section, micrometastases were found in 16 out of the 82 SLNs, upstaging 14 out of 31 patients (45%), from cN0 to pN⁺. Furthermore, a total of 1295 lymph nodes from the neck dissection specimens were analyzed, confirming only one more metastatic disease. Sensitivity and negative predictive value of SLN's biopsy were 93% and 94%, respectively, for frozen-section analysis. A study by Terada et al. (43) has shown frozen-sections analysis of the SLN to be superior to imprint cytology for detecting micrometastasis to SLN in clinically negative neck oral cancer.

D. Mucosal Surfaces of the Head and Neck

Frozen sections are especially useful for the distinction between an inflammatory and neoplastic lesion of the mucosa of the head and neck. In addition to infections by acid-fast organisms, fungal disease, such as histoplasmosis, blastomycosis, or actinomycosis, may be responsible for chronic ulcerative lesions of the mouth, oropharynx, and larynx. The demonstration of a granulomatous process, rather than a neoplastic one, in a given biopsy specimen requires a special procedure for identification of the pathogen (Fig. 8).

Immediate microscopic determination by frozen section of the depth of invasion of a carcinoma of the mucous membrane at any site is easy and useful; it is particularly necessary in deciding whether or not a neck dissection is necessary in a patient with a clinically N0 neck. Conversely, histologic grading of a squamous carcinoma should not be attempted in frozen sections; classification of the carcinoma as high, low, or intermediate grade is unlikely to be successful because of sampling limitations at the time of primary surgery and artifacts introduced by the procedure.

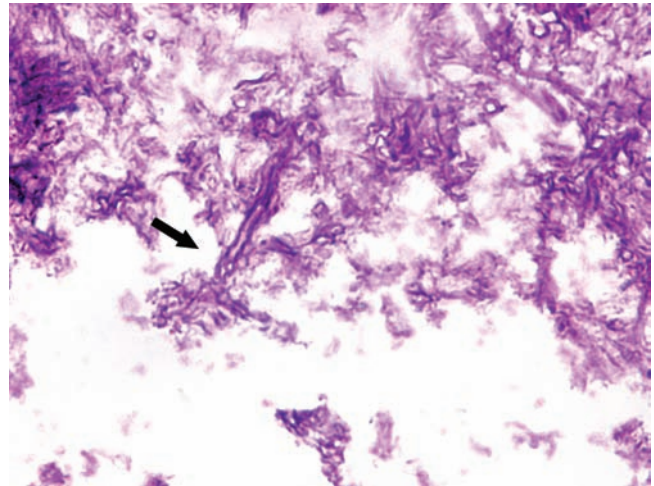


Figure 8 Fungal organisms clearly apparent in frozen section (arrow), permitting to perform special procedures for identification (cryostat-prepared section, H&E stained).

False-positive diagnoses are not uncommon in previously irradiated mucosal tissues (44). Postirradiation epithelial changes are misinterpreted as either carcinoma in situ or superficially invasive carcinoma. Immediate preoperative irradiation leads to no such problems, although days to years later, a range of changes appear, some of which are a source of confusion if unrecognized. Irradiation fibroblasts are large cells with hyperchromatic atypical nuclei, usually recognizable by being scattered in scar or inflammatory tissue and not forming a coherent cellular grouping after the manner of a sarcoma (45). Telangiectasia, bizarre striated muscle degeneration, and pseudoepitheliomatous proliferation of mucosal glands or their ducts are other changes observed after irradiation (45). Familiarity with these unusual cytologic and histologic features would preclude misinterpretation by the pathologist. In view of their importance, it should be a rule that the pathologist is to be informed when the specimen submitted for examination has been previously irradiated (44,45).

E. Salivary Gland

Frozen-section diagnoses of tumors of the parotid and submandibular salivary glands present no more serious problems than do frozen-section diagnoses of tumors elsewhere in the body (46–51). The false-positive rate for frozen-section malignancy has been reported in the range of 0% to 12% and the false-negative rate 11% to 0% (46–48). With the advent of fine-needle aspiration (FNA), the need for frozen section has shifted from diagnosis to assessment of margins of resection, checking suspicious lymph nodes and nerve invasion (46,48). Also, frozen section is requested for diagnostic confirmation of an FNA that is called nondiagnostic or benign but still believed

to be clinically suspicious for malignancy (48). The plan for surgical treatment for malignant tumors of the parotid and submandibular glands is based primarily on clinical staging, rather than on the histologic type (52–54).

Generally, one should not have trouble identifying the common tumors. The most difficult differential diagnoses, regardless of the salivary site, are (i) distinguishing mucoepidermoid carcinoma from chronic sialadenitis and from necrotizing sialometaplasia (Fig. 9), (ii) distinguishing some monomorphic adenomas from adenoid cystic carcinoma, and (iii) distinguishing some low-grade adenoid cystic carcinomas from pleomorphic adenomas.

Resection of the facial nerve is not dependent on the histologic subtype of a parotid neoplasm. It is based on the gross anatomic intimacy of a parotid neoplasm to the nerve (55). The extent of parotidectomy is also less guided by histologic type than by size and extensions, especially when a definitive biopsy specimen is obtained by subtotal parotidectomy with

removal of the tumor. To seek guidance on the basis of a frozen section of salivary gland tumor so that a neck dissection might be performed in a patient with a neck clinically negative for disease is to lack an appreciation and knowledge of the frequency of nodal metastasis in the more commonly encountered salivary gland malignancies: adenoid cystic carcinoma, acinic cell carcinoma, and low-grade mucoepidermoid carcinoma. None of this trio exhibits a high incidence of metastases to regional lymph nodes. High-grade carcinoma, such as the far less common primary squamous cell carcinoma, ductal carcinoma, and high-grade mucoepidermoid carcinoma, may warrant elective dissections of the neck; but this decision is principally surgical, not pathologic (52–54).

Margins in salivary gland tumors are relative to the glands involved. For the parotid gland, margin selection is facilitated by nearly 80% of the tumors occurring in the superficial lobe (lateral to the facial nerve) and the appropriate “biopsy” being a lateral lobectomy. The deep surface must be examined, and

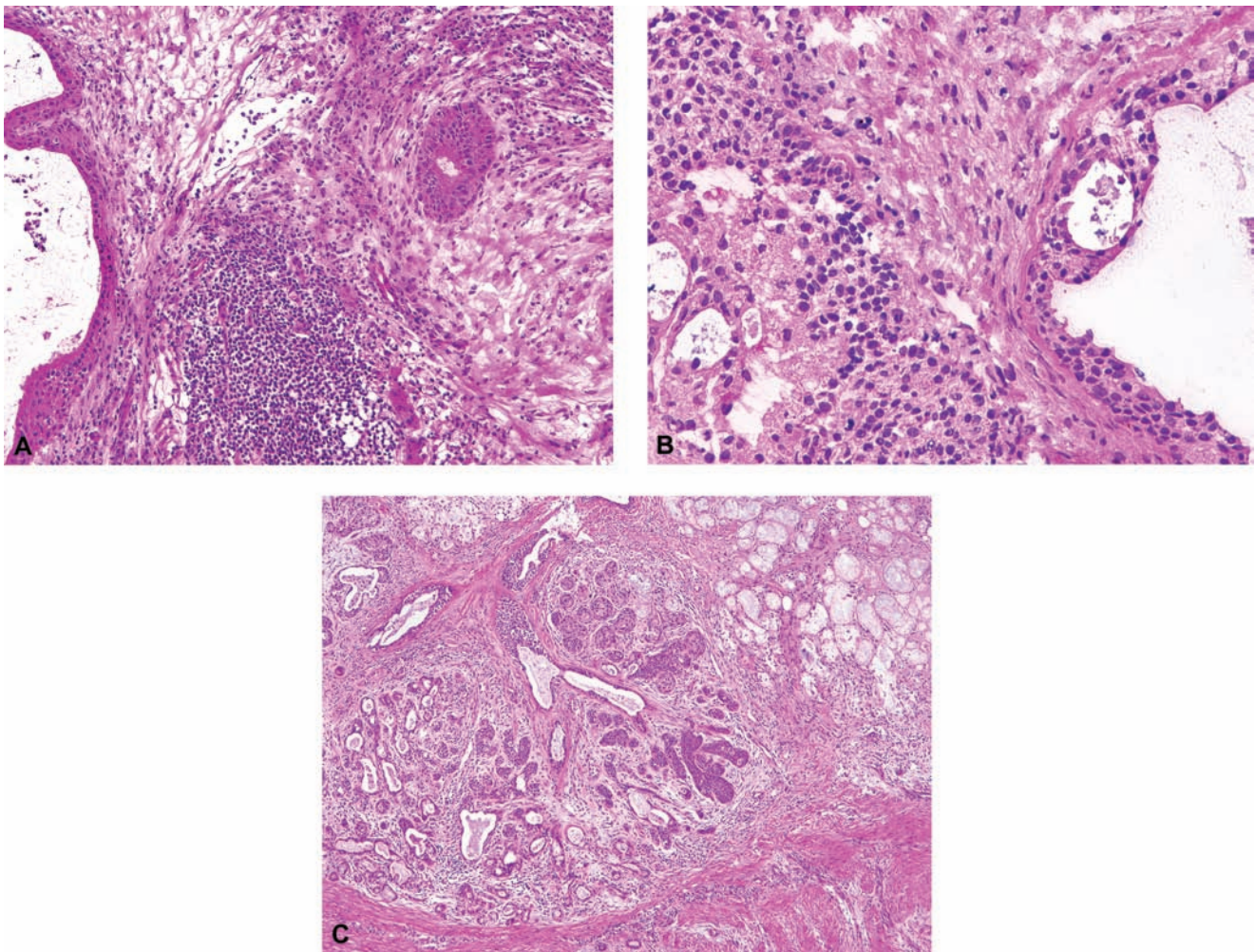


Figure 9 Frozen-section slides. (A) Chronic sialoadenitis (B) Low grade mucoepidermoid carcinoma (C) Necrotizing sialometaplasia (cryostat-prepared sections, H&E stained).

any suspicious extension beyond the capsule of the gland proper is required to be sectioned. Because the facial nerve is preserved in nearly all instances, except when it is grossly nondissectable from the tumor, the surgeon usually provides a specimen from near the nerve to discern any microscopic residual disease that could be treated by postoperative irradiation (53,55).

The appropriate operation for a submandibular salivary gland neoplasm is at least total removal of the gland. Sections from the superior (nearest the floor of mouth), lateral, and medial aspects, with deep and inferior margins, are necessary for the evaluation of extraglandular extension into adjacent soft tissues (54).

Margins for minor salivary gland tumors are similar to those for other mucosal lesions: depth and circumferential excision lines (56).

The often-variable microscopic appearance of salivary gland tumors in different areas gives rise to the possibility of erroneous sampling (46–48). To keep sampling error at a minimum, a careful gross examination of the specimen by the pathologist is imperative. Three important features of the gross specimen should be studied: First, what is the relation between the lesion and the adjacent normal salivary gland tissue? Sections submitted for frozen section should demonstrate this relation. A frozen section should be taken at the junction of tumor and apparently normal tissue rather than from the center of the neoplasm. Second, how far is the tumor from the surgical resection margins? A frozen section should be taken between the neoplasm and the closest line of excision. Third, are any lymph nodes involved by tumor? In parotid and submandibular gland tumors, lymph nodes are often included with the specimen. Any enlarged lymph node should be examined by frozen section.

In examining frozen sections of lymph nodes related to salivary glands, the pathologist must not mistake benign glandular inclusions for malignant tumors; heterotopic islands of salivary gland tissue may be found in paraparotid lymph nodes and, less frequently, in the upper cervical lymph nodes (see chap. 16). The pathologist, unaware of this phenomenon, may incorrectly interpret these as metastatic carcinomas in a frozen section. Lymphoid infiltrate is not unusual in some acinic cell carcinomas, mucocystic carcinomas, and monomorphic adenomas (see chap. 17).

Request for frozen-section diagnoses of lesions of the minor salivary glands requires especial interaction between the pathologist and surgeon. The surgeon must consider the possibility of resecting the lesion with a modest margin; further surgical treatment can easily be accomplished immediately if examination of the frozen section indicates the need. If the extent or location of the lesion precludes an excisional biopsy, an incisional biopsy and frozen-section diagnosis should be attempted. Under these circumstances, the pathologist should embed in toto and section at different levels all the material submitted for study. In biopsies of minor salivary gland tumors, sometimes only one of the levels will contain the characteristic microscopic areas that allow the pathologist to make a correct interpretation (56).

F. Thyroid Gland

The routine use of preoperative FNA biopsy has restricted the use of frozen-section examination for only the cases in which the needle biopsy was not diagnostic, when a previously unidentified nodule is detected during surgery, to evaluate surgical margins or for detecting cervical lymph node metastasis (57). Also, lesions suggestive of medullary carcinoma should be confirmed prior to completion of thyroectomy and possible bilateral anterior compartment lymph node dissection (57).

An acceptable risk taken by the pathologist includes the possibility of missing a minute papillary carcinoma on frozen section. It is not unusual that after a frozen-section diagnosis of benign tumor established on a lobectomy specimen, the following day when the sections of the remaining tissue are examined, a microscopic focus of papillary carcinoma is found elsewhere in the lobe (58). The same situation happens when in a multinodular goiter only the dominant nodule is sampled for frozen-section examination, a separate area taken for permanent study demonstrates a simultaneous malignancy (59).

Identification of the various types of thyroiditis, including Riedel's struma, is accomplished readily with frozen section (60). Because both Riedel's struma and granulomatous thyroiditis may be mistaken for cancers on gross examination, the use of the frozen-section technique is mandatory. Hashimoto's thyroiditis is less likely to resemble carcinoma, although it is sometimes confused grossly with lymphoma.

Papillary lesions of the thyroid gland seldom present difficulty in histopathologic diagnosis on frozen section. Papillary hyperplasia in adenomatous goiter and diffuse toxic goiter are easily distinguished from papillary carcinoma. Papillary carcinoma shows infiltrative growth into the capsule or surrounding thyroid gland and frequently contains psammoma bodies. On occasions, papillary carcinomas may not demonstrate obvious papillary formations and instead appear as broad, flat sheets of cells or a follicular pattern is observed. In those cases in which the possibility of papillary carcinoma exists and the morphologic characteristic of the tumor are distorted in the frozen sections, intraoperative touch imprints or scrape preparations are of great help (Fig. 10). Papillary structures, oval nuclei, nuclear enlargement, nuclear grooves, and inclusions are more easily recognizable on intraoperative cytology than on histologic frozen sections (60–62).

The distinction between follicular adenoma and well-differentiated, encapsulated follicular carcinoma may present more difficulty to the surgical pathologist. This distinction is possible only if one finds capsular or vascular invasion (60). If no invasion is recognized, the lesion is considered benign. If atypical features are present, the lesion is then classified as of "uncertain malignant potential" (63). To provide relevant information to the surgeon in this situation, the entire capsule must be submitted for microscopic examination at the time of frozen section, a tedious and too often nonproductive endeavor. When the

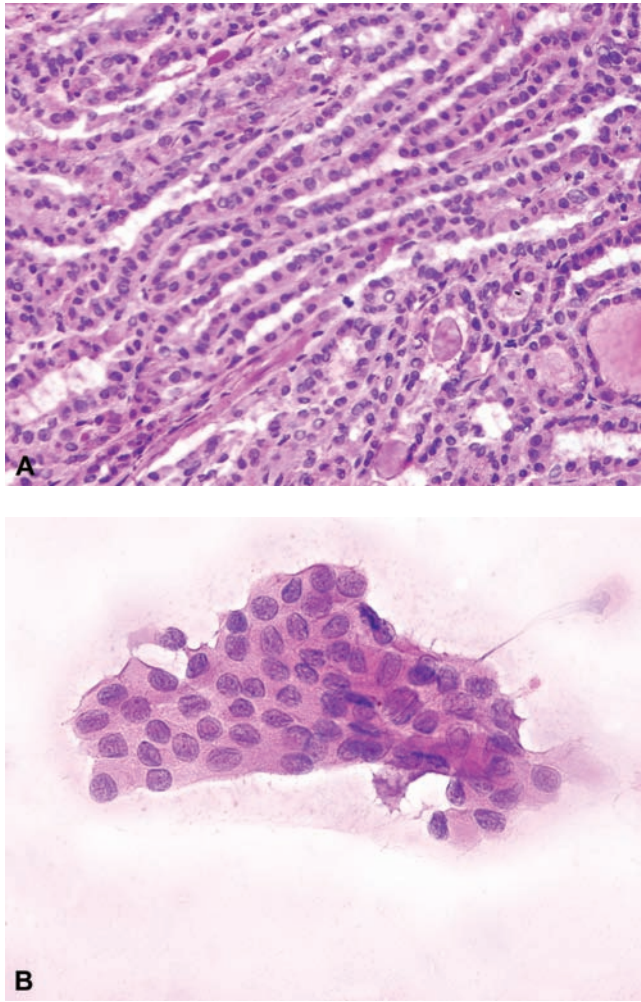


Figure 10 H&E-stained preparations. (A) Cryostat-prepared section of papillary carcinoma with trabecular pattern note the lack of nuclear characteristics. (B) Intraoperative cytologic imprint showing nuclear features diagnostic of papillary carcinoma. *Abbreviation:* H&E, hematoxylin and eosin.

pathologist is faced with this dilemma at the time of surgery, some authors recommend that only three blocks from the capsule-thyroid interface should be examined by frozen section (64). Often this is inadequate and the diagnosis is deferred, because invasion is not often identified on frozen sections (63,64). In a review by Callcut et al. (64), 152 patients underwent surgical resection for follicular lesions, 32% (41) were reported as benign, 4% (5) as malignant, and 2% (3) as indeterminate, and in 62% (80), the diagnosis was deferred to permanent histology. On paraffin section, all patients with malignant frozen section had had thyroid carcinoma, and all 41 patients with benign frozen section had benign lesions. The authors concluded that "frozen sections analysis for follicular lesions seems to be highly specific and accurate. However, because of the low sensitivity, routine use of frozen section is not cost effective in patients with

follicular thyroid lesions." The diagnosis of Hurthle cell carcinoma by frozen-section examination involves the same type of questions as the encapsulated, well-differentiated follicular carcinoma (63). Here again, adequate evaluation of the capsule-thyroid interface is mandatory; this may necessitate histologic examination of the entire border of the neoplasm (60).

The pathologist must remember that invasion of muscle by nonneoplastic thyroid follicles can take place in extreme degrees of toxic hyperplasia and that, sometimes, apparently benign thyroid tissue can be implanted within the lateral neck during thyroid surgery or blunt trauma (65). In the former case, the clinical history and the absence of abnormal nuclei distinguish Graves' disease from follicular carcinoma. In the latter the previous history, the microscopic pattern of the tissue, and the presence of suture material are helpful in ruling out cancer.

We must remind ourselves that, during the development of the thyroid gland, small nodules of the gland may become detached from the thyroid proper. These nodules may show the same pathologic changes that take place in the gland proper (thyroiditis, hyperplasia, and nodular goiter) (60). At surgery, the discovery of such a nodule in the immediate vicinity of the gland may lead the surgeon to believe that he or she is dealing with metastatic tumor. If one of the nodules is submitted for frozen-section examination, the pathologist may mistake this nodule of chronic thyroiditis for metastatic thyroid carcinoma in a lymph node.

An uncommon problem is the distinction between thyroid and parathyroid tissue. This may require permanent sections for immunocytochemical techniques for demonstration of parathyroid hormone or thyroglobulin. Here again the preparation of intraoperative touch imprints are of great help (21,23).

G. Parathyroid Gland

With the advent of preoperative radionucleotide scanning using technetium-99m sestamibi scanning (MIBI) and intraoperative quick parathyroid hormone (QPTH) monitoring to identify abnormal hyperfunctioning parathyroid glands, the role of the frozen section in the intraoperative diagnosis of abnormal parathyroid glands once again has been called into question. Some authors have espoused the superiority of intraoperative hormone assays over frozen section, as the results of these tests inform the operating surgeon when the hyperfunctioning parathyroid tissue has been removed (57,66–68). Furthermore, an experienced parathyroid surgeon doing a classic exploration on an unexplored neck can usually make the distinction between parathyroid tissue and other tissues (lymph nodes and thyroid) without a pathologist's assistance (67).

Dewan et al. (67) analyzed 50 parathyroidectomies performed by a single surgeon. Diagnoses on gross examination of both the surgeon and pathologist were recorded, cytologic smears made, and frozen sections performed. Of the 50 cases (35 adenomas

and 15 hyperplasias), both the surgeon's and pathologist's opinions on gross examination were concordant. Incorrect gross identification occurred by both in 6% (3) of the cases. They concluded that experienced parathyroid surgeons need not routinely request frozen-section examination for tissue confirmation, especially with the use of MIBI and QPTH assays. According to these authors, the situations that warrant the judicious use of frozen section would include the following: (i) the infrequent parathyroid carcinoma, (ii) cases of multiple gland disease (primary, secondary, or tertiary hyperparathyroidism), (iii) ectopic gland location, (iv) reoperant necks, (v) otherwise technically difficult primary surgeries, and (vi) atypical parathyroid appearance (small, firm, or ectopic location).

The rarely encountered parathyroid carcinoma is identified largely by its invasion of adjacent structures (69–71). Questions are more likely to arise in the distinction between nonmalignant pathologic processes in the gland (69,70). Parathyroid histopathologic interpretation of an adenoma versus hyperplasia is considered by many pathologists to be a persistent challenge (67).

The size of the parathyroid tumor is a factor in its identification. A large tumor requires only a section for its recognition as a parathyroid adenoma. To determine whether a slightly enlarged parathyroid is an adenoma or not depends on its weight, usually combined with examination of a histologic section to establish the presence or absence of (i) fatty stroma, (ii) an encapsulated nodule or mass with a small rim of compressed normal tissue, and (iii) the presence of cells with giant nuclei (70). These are not absolute criteria. Furthermore, on frozen section, the criteria for adenoma are seldom identified; hence, the differentiation between adenoma and hyperplasia is not based on pathologic criteria, but on operative findings; optimally, all parathyroid adenomas should be identified (57,69). Successful operations have been shown to be strongly associated with experience of the surgeon, with cure rates of 95% to 98% after neck exploration and identification of all parathyroid glands (57). Biopsy of each parathyroid is not necessary and may lead to postoperative hypoparathyroidism.

Intracytoplasmic cytologic examination is of great help during intraoperative consultation to improve the diagnostic accuracy of parathyroid adenoma. Sasano et al. used air-dried Wright-Giemsa-stained imprints and smears to demonstrate the presence of intraparenchymal and intracellular fat (72). The cells of the parathyroid adenomas do not contain extra or intracellular lipid, whereas the cytologic material from normal or atrophic parathyroid glands has large amounts of intracellular lipids and variable amounts of extracellular lipid. They advocated that this procedure is much more rapid, much easier, and less labor intensive than using conventional frozen sections with special stain procedures for fat staining.

Although there have been numerous studies (17–20,23) on the use of cytology in evaluating of parathyroid tissue, little attention has been paid to

the accuracy of this methodology. The studies of Yao et al. (73) revealed that cytology does not provide the accuracy needed in the operating room, where very near 100% is required. A misinterpretation rate of 31% in identifying parathyroid and 44% in identifying thyroid is not acceptable. This study provides additional support for the use of the standard frozen-section technique adjunct of cytology imprints and smears in the intraoperative pathologic evaluation of tissue during cervical exploration for primary hyperparathyroidism (57,66).

Although the combination of size and color usually identifies a parathyroid gland as such, sometimes a parathyroid gland may be inadvertently devascularized during thyroid surgery. In these instances, biopsies of possible parathyroid tissue may be submitted to the pathologist for proper identification by the frozen-section technique before autotransplantation (57,69) (Figs. 11,12).

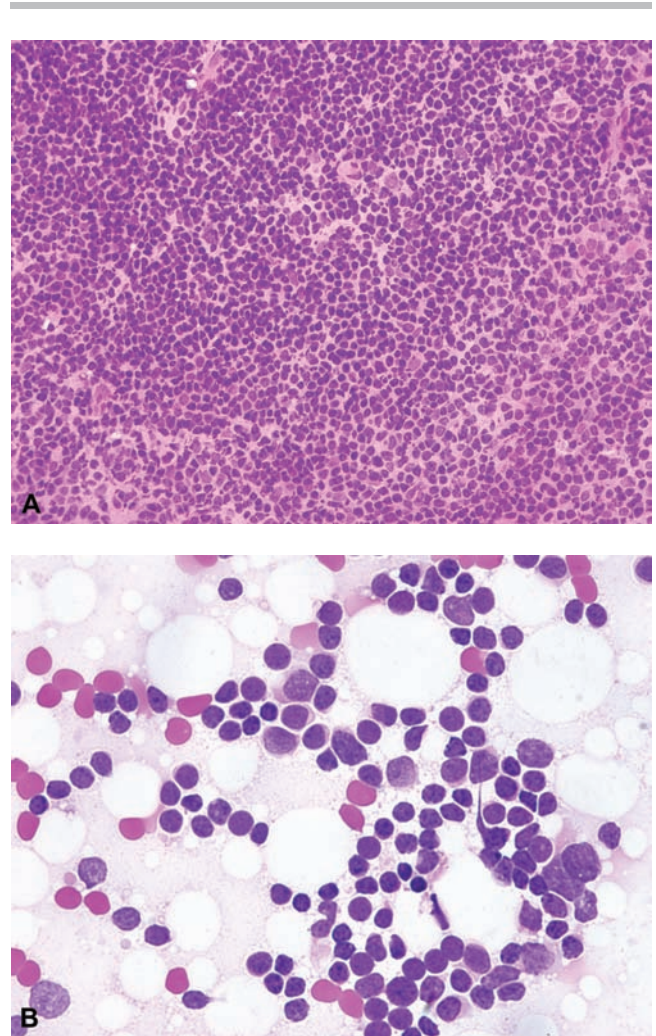


Figure 11 Cryostat-prepared section and intraoperative cytology (A,B) of lymphoid tissue submitted as possible parathyroid. (A) Frozen section artifacts may simulate solid pattern of parathyroid gland. (B) Imprint showing cells with diagnostic features of lymphoid cells.

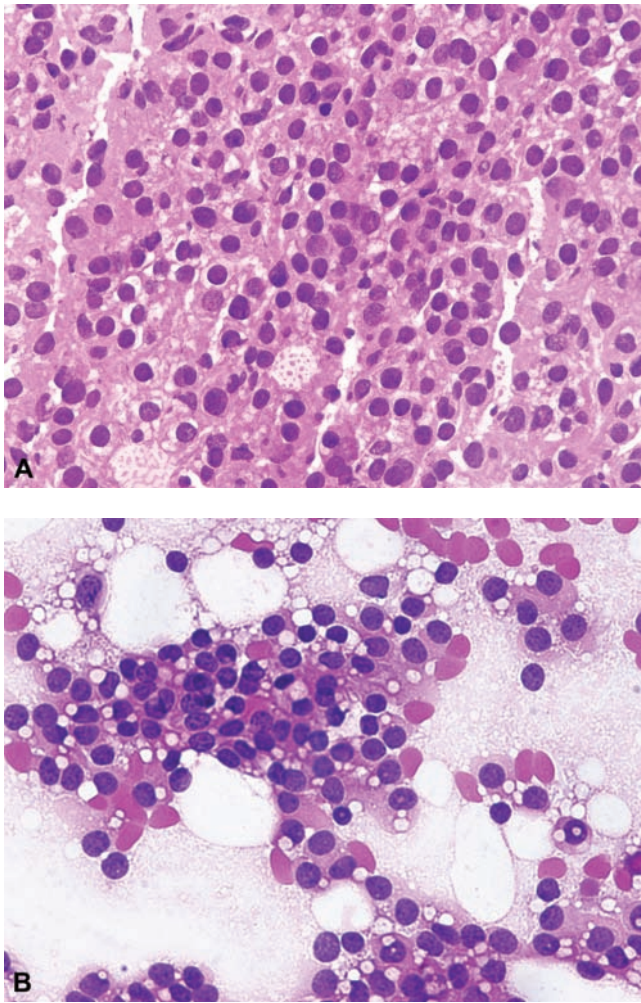


Figure 12 Cryostat-prepared section and intraoperative cytologic imprint of parathyroid adenoma (A,B). (A) Frozen section showing solid pattern of parathyroid adenoma with a few microfollicles (H&E). (B) Numerous chief cells and rare oxyphilic cells on intraoperative cytologic imprint (H&E). *Abbreviation:* H&E, hematoxylin and eosin.

REFERENCES

- Gal AA. The centennial anniversary of the frozen section technique at the Mayo Clinic. *Arch Pathol Lab Med* 2005; 129(12):5132–1535.
- Wright JR Jr. The development of the frozen section technique, the evolution of surgical biopsy, and the origins of surgical pathology. *Bull Hist Med* 1985; 59(3):295–326.
- Ibanez ML, Russell WO, Chang JP, et al. Cold chamber frozen sections for operating room diagnosis and routine surgical pathology. *Lab Invest* 1960; 9(1):98–109.
- Dahlin DC. Seventy-five years of experience with frozen section at the Mayo Clinic. *Mayo Clin Proc* 1980; 55(11):721–723.
- Unni KK. Practice of frozen section pathology at the Mayo Clinic. *Int Pathol* 1996; 37(1):1–2.
- Dehner LP, Rosai J. Frozen section examination in surgical pathology. *Minn Med* 1977; 60(2):83–94.
- Wendum D, Flejon JF. Quality assessment of intraoperative frozen section in a teaching hospital: an analysis of 847 consecutive cases. *Ann Pathol* 2003; 23(5):393–399.
- Oneson RH, Minke JA, Silverberg SG. Intraoperative pathologic consultation: an audit of 1000 recent consecutive cases. *Am J Surg Pathol* 1989; 13(3):237–243.
- Novis DA, Gephart GN, Zarbo RJ. Interinstitutional comparison of frozen section consultation in small hospital. A college of American Pathologists Q-Probes Study of 18532 frozen section consultation diagnose in 233 small hospitals. *Arch Pathol Lab Med* 1996; 120(12):1087–1093.
- Nakazawa H, Rosen P, Lane N. Frozen section experience in 3000 cases. *Am J Clin Pathol* 1968; 49(1):41–51.
- Remsen KA, Lucente FE, Biller HF. Reliability of frozen section diagnosis in head and neck neoplasms. *Laryngoscope* 1984; 94(4):519–525.
- Bauer WC. The use of frozen sections in otolaryngology. *Trans Am Acad Ophthalmol Otolaryngol* 1974; 78(2):88–97.
- Gandour-Edwards RE, Donald PJ, Wiese DA. Accuracy of intraoperative frozen section diagnosis in head and neck surgery: experience at a university medical center. *Head Neck Surg* 1993; 15(1):33–38.
- Rogers C, Klatt EC, Chandrasoma P. Accuracy of frozen section diagnosis in a teaching hospital. *Arch Pathol Lab Med* 1987; 111(6):514–517.
- Sawady J, Berner JJ, Siegler EE. Accuracy and reasons for frozen sections: a correlative retrospective study. *Hum Pathol* 1988; 19(9):1019–1023.
- Saltzstein SL, Nahum AM. Frozen section diagnosis. Accuracy and errors, uses and abuses. *Laryngoscope* 1973; 83(7):1128–1143.
- Silverberg SG. Intraoperative cytology: promise, practice, and problems. *Diagn Cytopathol* 1995; 13(5):386–387.
- Owings RM. Rapid cytologic examination of surgical specimens: a valuable technique in the surgical pathology laboratory. *Hum Pathol* 1984; 15(7):605–614.
- Shidham VB, Gupta D, Galindo LM, et al. Intraoperative scrape cytology: comparison with frozen section using probabilities statistical method. *Diag Cytopathol* 2000; 23(2):134–139.
- Mair S, Lash RH, Suskin D, et al. Intraoperative surgical specimen evaluation: frozen sections analysis, cytologic examination, or both. A comparative study of 206 cases. *Am J Clin Pathol* 1991; 96(1):8–1.
- Taner F, Poyraz A, Salman B, et al. Using imprint and frozen sections in determining the surgical strategies for thyroid pathologies. *Endocr Regul* 2001; 35(2):71–74.
- Brogi E, Torres-Matundan E, Tan LK, et al. The results of frozen section, touch preparation, and cytological smears are comparable for intraoperative examination of sentinel lymph nodes: a study in 133 breast cancer patients. *Ann Surg Oncol* 2005; 12(2):173–180.
- Shidham VB, Asma Z, Rao RN, et al. Intraoperative cytology increases the diagnostic accuracy of frozen sections for the confirmation of various tissues in the parathyroid region. *Am J Clin Pathol* 2002; 118(6):895–902.
- Byers RM, Bland KI, Borlase B, et al. The prognostic and therapeutic value of frozen section determinations in the surgical treatment of squamous carcinoma of the head and neck. *Am J Surg* 1978; 136(4):525–528.
- Looser KG, Shah JP, Strong EW. The significance of positive margins in surgically resected epidermoid carcinomas. *Head Neck Surg* 1978; 1(2):107–111.
- Loree TR, Strong EW. Significance of positive margins I oral cavity squamous carcinoma. *Am J Surg* 1990; 160(4):410–414.
- Scholl P, Byers RM, Batasakis JG, et al. Microscopic cut-through of cancer in the surgical treatment of squamous cell carcinoma of the tongue. Prognostic and therapeutic implications. *Am J Surg* 1986; 152(4):354–360.

28. Ord R, Aisner S. Accuracy of frozen sections in assessing margins in oral cancer resection. *J Oral Maxillofac Surg* 1997; 55(7):663–669.
29. Batsakis JG. Surgical excision margins: a pathologist's perspective. *Adv Anat Pathol* 1999; 6(3):140–148.
30. Meier JD, Oliver DA, Varvares MA. Surgical margin determination in head and neck oncology: current clinical practice. The results of an international American Head and Neck Society member survey. *Head Neck* 2005; 27(11):952–958.
31. Black C, Zarowaya E, Marotti J, et al. Frozen section evaluation of head and neck margins. *Mod Pathol* 2006; 19(1):204A.
32. Woolgar JA, Triantafyllou A. A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection margins. *Oral Oncol* 2005; 41(10):1034–1043.
33. Bauer WC, Lesinski SG, Ogura JH. The significance of positive margin in hemilaryngectomy specimens. *Laryngoscope* 1975; 85(1):1–13.
34. Kerawala CJ, Ong TK. Relocating the site of frozen sections—is there room for improvement? *Head Neck* 2001; 23(3):230–232.
35. Forest LA, Schuller DE, Lucas JG, et al. Rapid analysis of mandibular margins. *Laryngoscope* 1995; 105(3):475–477.
36. Oxford LE, Ducic Y. Intraoperative evaluation of cortical bony margins with frozen-section analysis. *Otolaryngol Head Neck Surg* 2006; 134(1):138–141.
37. Ballantyne AJ, McCarten AB, Ibanez ML. The extension of cancer of the head and neck through peripheral nerves. *Am J Surg* 1963; 106(10):651–667.
38. Goepfert H, Ditchtel WJ, Medina JE, et al. Perineural invasion in squamous cell carcinoma of the head and neck. *Am J Surg* 1984; 148(4):542–547.
39. Garden AS, Weber RS, Morrison WH, et al. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995; 32(3):619–626.
40. Conrad GR, Sinha GR, Holzhauer M. Perineural spread of skin carcinoma to the base of the skull: detection with FDG PET and CT fusion. *Clin Nucl Med* 2004; 29(11):717–719.
41. Newlin HE, Morris CG, Amdur RJ, et al. Neurotropic melanoma of the head and neck with clinical perineural invasion. *Am J Clin Oncol* 2005; 28(4):399–402.
42. Tschopp L, Nuyens M, Stauffer E, et al. The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx. *Otolaryngol Head Neck Surg* 2005; 132(1):99–102.
43. Terada A, Hazgawa Y, Goto M, et al. Sentinel lymph node radiolocalization in clinically negative neck oral cancer. *Head Neck* 2006; 28(2):114–120.
44. Barney PL. Histopathologic problems and frozen section diagnosis in disease of the larynx. *Otolaryngol Clin North Am* 1970; 3(3):493–515.
45. Berthrong M, Fajardo LF. Radiation injury in surgical Pathology. Part II. Alimentary tract. *Am J Surg Pathol* 1981; 5(2):153–178.
46. Seethala RR, LiVolsi VA, Baloch ZW. Relative accuracy of fine needle aspiration and frozen section in the diagnosis of lesions of the parotid gland. *Head Neck* 2002; 27(3):217–223.
47. Badoual C, Rousseau A, Heudes D, et al. Evaluation of frozen section versus definitive pathologic diagnosis in 721 parotid gland lesions. *Virchows Arch* 2005; 447(2):192A.
48. Wong DS. Frozen section during parotid surgery revisited: efficiency of its applications and changing trend of indications. *Head Neck* 2002; 24(2):191–197.
49. Zbaren P, Nuyens M, Loosli H, et al. Diagnostic accuracy of fine needle aspiration cytology and frozen section in primary parotid carcinoma. *Cancer* 2004; 100(9):1876–1883.
50. Longuet M, Nallet E, Guedon C, et al. Diagnostic value of needle biopsy and frozen section histological examination in the surgery of primary parotid tumors. *Rev Laryngol Otol Rhinol (Bord)* 2001; 122(1):51–55.
51. Iwai H, Yamashita T, Izumikawa M, et al. Evaluation of frozen section diagnosis of parotid gland tumors. *Nippon Jigbiinkoka Gakkai Kaiho* 1999; 102(11):1227–1233.
52. Spiro RH. Diagnosis and pitfalls in the treatment of parotid tumors. *Semin Surg Oncol* 1991; 7(1):20–24.
53. Bell RB, Dierks EJ, Homer L, et al. Management and outcome of patients with malignant salivary gland tumors. *Oral Maxillofac Surg* 2005; 63(7):917–928.
54. Rinaldo A, Ferlito A, Pelliteri PK, et al. Management of malignant submandibular gland tumors. *Acta Otolaryngol* 2003; 123(8):896–904.
55. Guntinas-Lichius O, Klussmann JP, Schroeder U, et al. Primary parotid malignoma surgery with normal preoperative facial nerve function: outcome and long term postoperative facial nerve function. *Laryngoscope* 2004; 114(5):949–956.
56. Beckhardt RN, Weber RS, Zane R, et al. Minor salivary gland tumors of the palate: clinical and pathologic correlates of outcome. *Laryngoscope* 1995; 105(11):1155–1160.
57. Anton RC, Wheeler TM. Frozen section of thyroid and parathyroid specimens. *Arch Pathol Lab Med* 2005; 129(12):1575–1584.
58. Cetin B, Asian S, Hatiboglu C, et al. Frozen section in thyroid surgery: is it a necessity? *Can J Surg* 2004; 47(1):29–33.
59. Rios-Zambudio A, Rodriguez-Gonzalez JM, Sola-Perez J, et al. Utility of frozen section examination for diagnosis of malignancy associated with multinodular goiter. *Thyroid* 2004; 14(8):600–604.
60. LiVolsi VA, Merino JM. Histopathologic differential diagnosis of the thyroid. *Pathol Annu* 1981; 16(2):357–406.
61. Carcangui ML, Zampi G, Rosai J. Papillary thyroid carcinoma. A study of its many morphologic expressions and clinical correlates. *Pathol Annu* 1985; 2(1):1–44.
62. Furlan JC, Bedard YC, Rosen IB. Role of fine-needle aspiration and frozen section in the management of papillary thyroid carcinoma subtypes. *World J Surg* 2004; 28(9):880–885.
63. LiVolsi VA, Baloch ZW. Follicular neoplasms of the thyroid. View, biases and experience. *Adv Anat Pathol* 2004; 11(6):270–287.
64. Callcut RA, Selvaggi SM, Mack E, et al. The utility of frozen section evaluation for follicular thyroid lesions. *Ann Surg Oncol* 2004; 11(1):94–98.
65. Harach HR, Cabrera JA, Williams ED. Thyroid implants after surgery and blunt trauma. *Ann Diagn Pathol* 2004; 8(2):61–68.
66. Guarda LA. Rapid intraoperative parathyroid hormone testing with surgical pathology correlations: the “chemical frozen section”. *Am J Clin Pathol* 2004; 122(5):704–712.
67. Dewan AK, Kapadia SB, Hollenbeak CS, et al. Is routine frozen section necessary for parathyroid surgery? *Otolaryngol Head Neck Surg* 2005; 133(6):857–862.
68. Phillips IJ, Kurzawinski TR, Honour JW. Potential pitfalls in intraoperative parathyroid hormone measurements during parathyroid surgery. *Ann Clin Biochem* 2005; 42(6):453–458.
69. Westra WH, Pritcher DD, Udelsman R. Intraoperative confirmation of parathyroid tissue during parathyroid

- exploration; a retrospective evaluation of the frozen section. *Am J Surg Pathol* 1998; 22(5):538–544.
70. Grimelius L, Akerstrom G, Johansson H, et al. Anatomy and histopathology of human parathyroid glands. *Pathol Annu* 1981; 16(2):1–24.
71. DeLellis RA. Parathyroid carcinoma: an overview. *Adv Anat Pathol* 2005; 12(2):53–61.
72. Sasano H, Geelhoed GW, Sliverberg SG. Intraoperative cytologic evaluation of lipid in the diagnosis of parathyroid adenoma. *Am J Surg Pathol* 1988; 12(4):282–286.
73. Yao DX, Hoda SA, Yin DY, et al. Interpretative problems and preparative technique influence reliability of intraoperative parathyroid touch imprints. *Arch Pathol Lab Med* 2003; 127(1):64–67.

Diseases of the Larynx, Hypopharynx, and Trachea

Leon Barnes

*Department of Pathology, University of Pittsburgh Medical Center,
Presbyterian-University Hospital, Pittsburgh, Pennsylvania, U.S.A.*

I. VOCAL CORD NODULES AND POLYPS

A. Introduction

A vocal cord nodule or polyp (VCNP) represents a nonneoplastic, vascular-stromal reaction to vocal abuse. Some otolaryngologists distinguish nodules from polyps; those that do, define a nodule as a small sessile lesion, usually less than 3 mm, which occurs between the anterior and middle third of the true vocal cord. It is typically bilateral, symmetrical, and immobile during phonation (1–4). A polyp, in contrast, may be sessile or pedunculated, usually larger than 3 mm, and it occurs on the free edge of the anterior third of the true vocal cord. It is generally unilateral and, if pedunculated, mobile on phonation.

Data, however, indicate that vocal cord nodules and polyps are etiologically related and histologically identical, differing only in size. If left untreated, any nodule has the capacity to develop into a polyp. Distinguishing between the two lesions on the basis of the above criteria, therefore, has no merit or clinical significance. The two terms can be used interchangeably or according to one's bias.

In addition to focal lesions, the true vocal cord can also be involved diffusely, a rare condition referred to as diffuse polyposis or Reinke's edema.

Synonyms VCNPs include laryngeal nodule, screamer's nodule, singer's nodule, preacher's nodule, and corditis nodosa.

B. Etiology

Phonotrauma in the form of vocal overuse (excessive quantity of voice), abuse (yelling), and misuse (vocal hyperfunction with excessive muscular tension) is the chief factor in the pathogenesis of VCNPs (5; see "Pathology" below). Smoking, gastroesophageal reflux, atmospheric pollutants, and hypothyroidism may be additional contributing or aggravating factors (6). There is also some evidence to suggest that psychological factors may play a role. For instance, some investigators have observed that VCNPs are more common in individuals with vociferous and aggressive personalities and less frequent in those who are soft spoken, gentle, and more self controlled (2).

C. Clinical Features

VCNPs affect both sexes and all age groups, with a peak incidence between 20 and 50 years of age. Presenting symptoms range from "breaking" of the voice to hoarseness. Patients often report that their voice fatigues easily, and that it is typically best first thing in the morning and deteriorates with prolonged speaking or singing (2). Some describe a constant desire to cough or clear the throat. Airway compromise is not a significant issue. The size of the lesion does not always correlate with the extent of the vocal disability. At laryngoscopy, VCNPs appear as white, pearly gray, tan, or red growths that rarely exceed 15 mm in greatest dimension (Fig. 1). As the name implies, they occur only on the true vocal cords and nowhere else in the larynx. While they may appear anywhere on the true vocal cord, most occur on the free edge at the junction of the anterior and middle thirds. This site corresponds to the middle of the membranous cord and represents the maximum point of vibratory impact during speaking and singing.

They are equally distributed between the right and left vocal cords and are sometimes multiple and/or bilateral. Although otolaryngologists are highly adept in recognizing VCNPs, other conditions such as "keratosis," squamous papilloma, or even amyloid may be mistaken for these lesions.

D. Pathology

The pathology takes place in the free edge of the true vocal cord in the space of Reinke (7–9). This space is roughly triangular and is bounded superiorly by the superior arcuate line (which represents the junction of the squamous epithelium of the true vocal cord with the respiratory epithelium of the ventricle) and inferiorly by the inferior arcuate line (which represents the junction of the squamous epithelium of the true vocal cord with the respiratory epithelium of the subglottis). The medial border is the vocalis muscle. The space of Reinke, therefore, corresponds basically to the lamina propria of the true vocal cord and, as such, contains loose fibrous tissue and blood vessels.

Five histologic types of VCNPs are recognized: (i) edematous-myxoid, (ii) fibrous, (iii) hyaline ("amyloid-like"), (iv) vascular, and (v) mixed. It is speculated that

vocal abuse leads to mechanical trauma of the cords as a result of vibration with excessive friction and forceful opposition on adduction (10,11). This, in turn, leads to increased vascular permeability with leakage of contents into the stroma (Fig. 2). If only fluid escapes, an edematous-myxoid VCNP is formed,

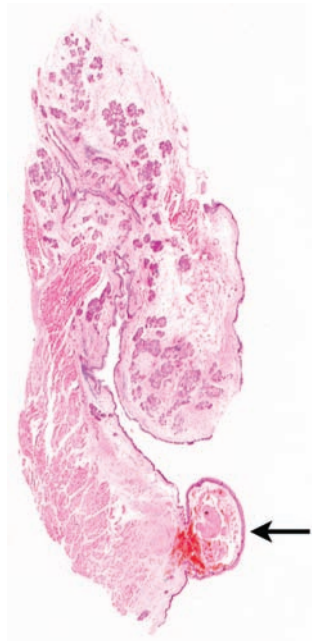


Figure 1. Typical appearance of a vocal cord nodule-polyp (arrow) (H&E, whole mount).

PATHOGENESIS OF VOCAL CORD NODULES

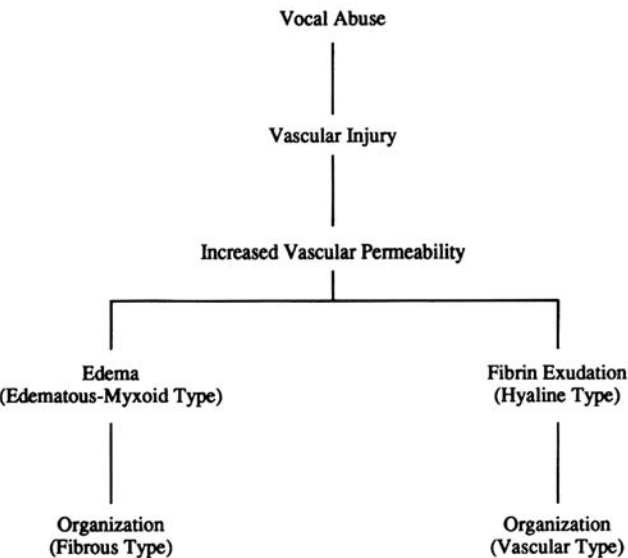


Figure 2. Pathogenesis of vocal cord nodules-polyps.

which, if not removed, eventually undergoes fibrosis creating the fibrous variant of a VCNP (Figs. 3 and 4). If the vascular injury is more severe, fibrin escapes creating the hyaline variant of a VCNP (Fig. 5). In an attempt to organize the extravasated fibrin, as in any blood clot, there is an ingrowth of new blood vessels transforming the hyaline stage into a vascular VCNP (Fig. 6). VCNPs with two or more of the above patterns (mixed type) are not uncommon (Fig. 7).

The epithelium overlying a VCNP may be normal, hyperplastic, atrophic, ulcerated, keratotic, parakeratotic, or even mildly dysplastic. These changes, however, have no clinical significance. Thickening and hyalinization of the basement membrane is also common but inflammatory cells are absent, unless the VCNP is ulcerated. Hemosiderin may also be seen.

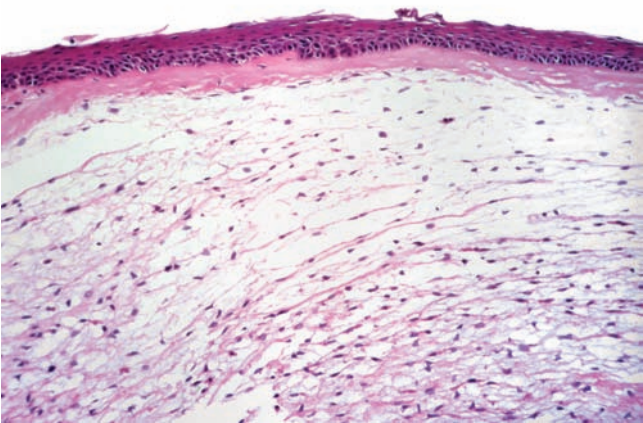


Figure 3. Vocal cord nodule-polyp, edematous-myoid stage (H&E, 200 $\times$). Note the loose, edematous stroma.

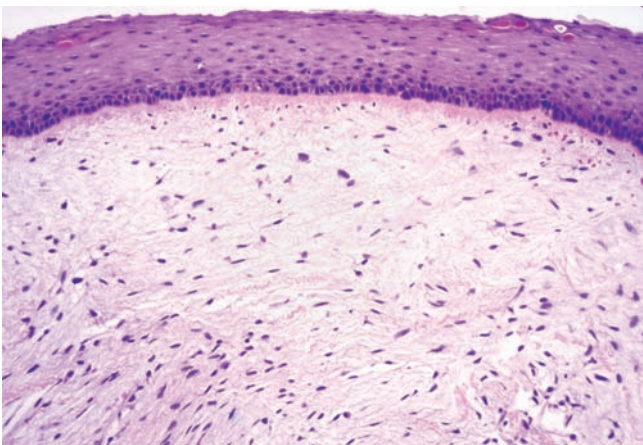


Figure 4. Vocal cord nodule-polyp, fibrous stage (H&E, 200 $\times$). The stroma is now more fibrous and is often mistaken for a fibroma.

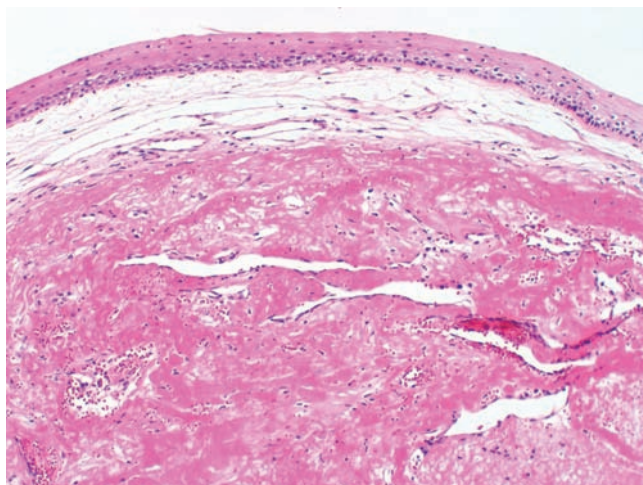


Figure 5. Vocal cord nodule-polyp, hyaline stage (H&E, 200 $\times$). Note the stromal exudation of fibrin.

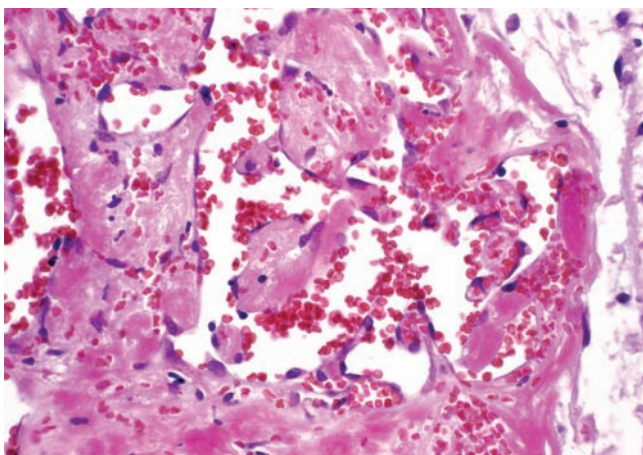


Figure 6. Vocal cord nodule-polyp, vascular stage (H&E, 400 $\times$). There is an ingrowth of blood vessels (*open spaces*) in an attempt to organize the extravasated fibrin.

E. Differential Diagnosis

The edematous-myxoid, fibrous, hyaline, and vascular VCNP are often mistaken, respectively, for myxomas, fibromas-neurofibromas, amyloid, and hemangiomas. Myxomas of the larynx are extremely rare, arise in the supraglottic larynx, are usually over 3 cm in size, are histologically relatively avascular, and are not covered by surface epithelium (12). In contrast, myxoid VCNP always arise on the true cord, are less than 15 mm in size, are well vascularized, and are covered by a mucous membrane. Fibromas of the true vocal cord are also rare and more densely collagenized than the fibrous VCNP. Neurofibroma can be excluded by

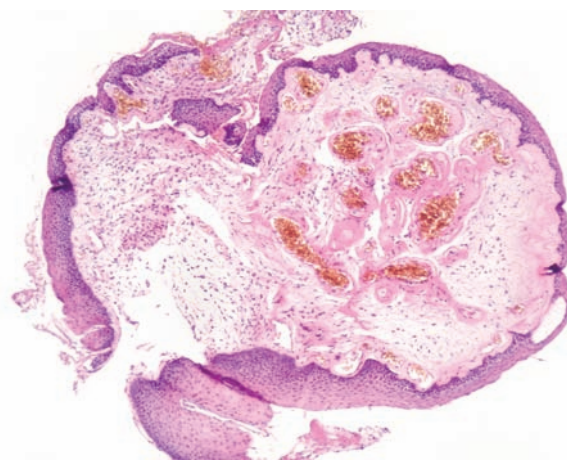


Figure 7. Vocal cord nodule-polyp, mixed stage (H&E, 40 $\times$). Note the edematous, hyaline and vascular components.

the fact that it is positive for S-100 protein, while the fibrous VCNP is negative. Mast cells can be seen in both lesions but tend to be more prominent in the neurofibroma. Amyloid can be distinguished from the hyaline VCNP by the fact that amyloid will show apple green birefringence with the Congo red stain when viewed under polarized light and will be negative with stains for fibrin. Vascular VCNP are separated from hemangiomas by the large amount of extravascular fibrin. Fibrin, if seen in hemangiomas, is always intravascular. In addition, hemangiomas of the larynx occur almost always in the supraglottic or subglottic larynx; they are distinctly uncommon on the true vocal cords.

F. Treatment and Prognosis

Although some VCNP may resolve spontaneously with voice counseling, others require surgical excision (2,5,6,13). New lesions may develop if vocal abuse is not curtailed, hence the need for counseling.

II. CONTACT ULCER, CONTACT GRANULOMA, INTUBATION GRANULOMA

A. Introduction

Contact ulcers, contact granulomas, and intubation granulomas are essentially synonyms for a spectrum of nonspecific pathologic changes that are etiologically related to vocal abuse, gastroesophageal reflux, and intubation (1–16). Smoking, excessive alcoholic intake, and repeated episodes of coughing and throat clearing may be additional or aggravating factors (11).

B. Clinical Features

They characteristically occur on the posterior third of the true vocal cord, usually in the area of the vocal

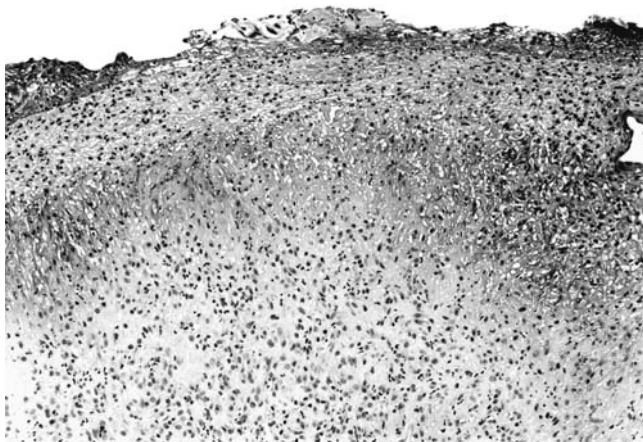


Figure 8. Contact ulcer (H&E, 100×). The ulcer is nonspecific, but when correlated with the site (posterior true vocal cord) and clinical history, the correct diagnosis can usually be made.

process of the arytenoid cartilage. The predilection for this site probably stems from the fact that the mucoperichondrium in this region is very thin and tightly bound with minimal subepithelial connective tissue. This anatomic arrangement allows for little mobility of the epithelium so that abrasion from intubation or repeated forceful abuse of the voice may result in ulceration.

Hoarseness, as might be expected, is the most common presenting symptom. Others include dysphagia, sore throat, sensation of a foreign body in the throat, dysphonia, choking, and pain.

The lesions may be unilateral or bilateral and present on laryngoscopic examination as a surface irregularity, an ulcer, or as a tan, yellow, or red polypoid or pedunculated mass from 1 to 30 mm (Figs. 8 and 9). Some are visible on computerized tomography and may be associated with sclerosis of the underlying arytenoid cartilage (11).

They occur in all age groups, but tend to be uncommon in children. In general, those lesions that are related to vocal abuse and reflux are more common in males, while those associated with intubation are more often seen in females. The smaller size of the female larynx and the fact that the mucoperichondrium overlying the arytenoid cartilage is also thinner in the female than the male (59 vs. 97 μ m in thickness) probably accounts for the predominance of intubation granulomas (4).

Considering the extent to which endotracheal intubation is practiced, intubation granulomas are rare. The incidence in all surgical patients has varied from 1 in 800 to 1 in 20,000 patients (4). The incidence is higher, however, in patients confined to intensive care. This is not unexpected since these patients are sicker and often have prolonged intubation. The "granuloma" may develop weeks to months after intubation. In a review of 35 cases, Howland and Lewis noted the interval from operation (intubation)



Figure 9. Intubation granuloma (polypoid granulation tissue). Gross and cut surface.

to the development of the "granuloma" varied from 2 to 28 weeks, with the majority appearing by the eighth week (1).

C. Pathology

The histologic changes are nonspecific and range from mucosal ulceration with marginal epithelial or pseudoepitheliomatous hyperplasia to a polypoid accumulation of granulation tissue. At times, the mucosa may even be intact but hyperplastic. Bacterial and fungal contamination of the ulcers is not uncommon and may be responsible for progressive "activity" of the lesion. Although the histologic findings are nonspecific, the characteristic location (posterior true vocal cord) coupled with the clinical history should suggest the correct diagnosis.

The mass of granulation tissue is often erroneously referred to as a "granuloma" or mistaken for a "pyogenic granuloma" (Fig. 9). Aside from the possible occurrence of a few scattered multinucleated giant cells, granulomas are not seen. Accordingly the term "granuloma" is not only inappropriate but misleading since it suggests the possibility of an infectious lesion. Pyogenic granuloma is now recognized to be a specific hemangioma, namely a lobular capillary hemangioma (17). The lobular arrangement of the capillaries in this lesion distinguishes it from the radial arrangement of capillaries in granulation tissue (Fig. 10).

D. Treatment and Prognosis

Once the diagnosis is established, therapy is directed at the underlying cause: voice counseling for vocal abuse, medical therapy for acid reflux, and endoscopic-laser excision for unresponsive lesions. Local recurrences, however, are not uncommon.

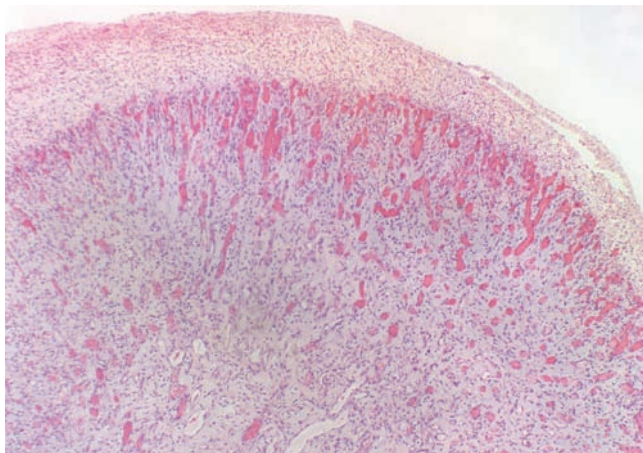


Figure 10. Intubation granuloma (H&E, 40 $\times$). The lesion consists of polypoid granulation tissue and is often referred to as a “pyogenic granuloma.” Note the radial arrangement of the capillaries. In “pyogenic granuloma (lobular capillary hemangioma),” the capillaries are arranged in lobules.

III. TEFLON GRANULOMA (TEFLONOMA)

A. Introduction

Patients with unilateral vocal cord paralysis experience difficulties in speaking and controlling their secretions. To restore glottic competence and correct these deficiencies, Teflon (polytetrafluoroethylene) is often injected into the atrophic, paralyzed vocal cord in order to expand the cord toward the midline to approximate the contralateral functioning cord (1–3) (Fig. 11).

The injected Teflon is in the form of a paste consisting of 50% Teflon and 50% glycerin, and is administered through a syringe and needle (4,5). Normally about 0.20 to 0.75 cc is injected (4).

B. Pathology

In tissue, Teflon appears as roughly round to ovoid, 50 to 100 μ m particles with clear centers and prominent dark borders that are birefringent under polarized light (Fig. 12). For the first three to five days after injection, there is a marked edematous and neutrophilic response to the particles, followed over the next several days by a decrease in neutrophils and a progressive increase in chronic inflammatory cells and multinucleated foreign body giant cells (6). Over the ensuing three to six months, fibrosis and foreign body giant cells become more prominent and chronic inflammation gradually ceases to exist (4). By six months of age, the lesion has normally reached histologic maturity. A few, however, may continue to enlarge beyond this date (5).

C. Differential Diagnosis

To the unwary, Teflon granulomas are sometimes mistaken for gouty tophi. The basically round to

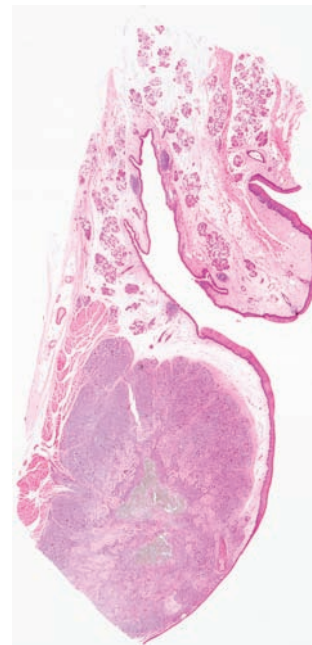


Figure 11. Vertical section through the laryngeal glottis. Teflon has been injected into the true vocal cord (H&E, 4 $\times$).

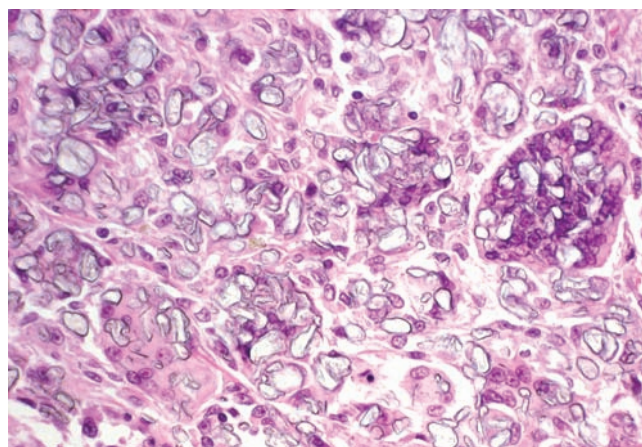


Figure 12. Teflon particles associated with a prominent multinucleated foreign body giant cell reaction. Insert shows characteristic round to ovoid Teflon particles with thick border and clear centers (H&E, 200 $\times$).

ovoid Teflon particles with clear centers and dark borders however contrast with the thin, elongated sodium urate crystals of gout. In addition, urate crystals stain positive (black) with the de Galantha stain, but only if the specimen has been prefixed in absolute alcohol. Urate crystals are water-soluble and will dissolve in most formalin-based fixatives. Patients with gout will also have elevated serum uric acid

levels. Particles of Teflon can also be identified, sometimes unexpectedly, on fine needle aspirates of neck masses (6).

D. Treatment and Prognosis

Although Teflon is not carcinogenic, at least in the larynx, therapeutic misadventures have been documented in about 2% to 10% of injections (6,8–13). Most complications are due to overinjection of the vocal cord or from inadvertent injection in sites other than the true vocal cords. These complications often result in exacerbation of previous symptoms, airway obstruction, or the formation of a laryngeal or neck mass (Teflon granuloma, Teflonoma) that can be mistaken for a neoplasm (10,14,7). Teflon can also migrate from the larynx to the region of the thyroid gland and masquerade as a thyroid tumor. Experimental evidence in dogs also indicates that Teflon particles can even migrate or embolize to cervical lymph nodes (15).

Surgical removal of Teflon granulomas often results in improvement or disappearance of all related symptoms. Attempts, however, to remove these granulomas endoscopically from the vocal cords may at times prove difficult and require several procedures (5). In these instances, the quality of the voice may deteriorate and be even worse than that before Teflon injection (16).

IV. SUBGLOTTIC STENOSIS

A. Introduction

Subglottic stenosis (laryngotracheal stenosis) may be congenital or acquired (1–4). Causes of the acquired type include trauma (intubation), infections (rhinoscleroma), neoplasms (chondrosarcoma), and local and systemic diseases (gastrointestinal reflux, amyloidosis, Wegener's granulomatosis). If no etiology is found, the term "idiopathic subglottic stenosis" is used.

B. Clinical Features

Subglottic stenosis occurs in all age groups and presents as progressive airway obstruction, often with associated voice changes. For reasons unknown, the idiopathic form is decidedly more frequent in women (80–94% of all cases) (4,5).

The typical lesion is circumferential and varies in length from a few millimeters to about 5 cm. The narrowing begins just beneath the true vocal cords and dramatically increases in severity as the cricoid cartilage is approached. The point of maximum stenosis is usually found at the level of the cricoid cartilage and upper trachea (5).

C. Pathology

The pathology depends, to a large extent, on the etiology—intubation, infections, amyloid, and neoplasms (see "Contact Ulcer, Contact Granuloma, Intubation Granuloma" above). Infrequently, Wegener's

granulomatosis will present as isolated subglottic stenosis and, in this instance, testing of the serum for the presence of antineutrophil cytoplasmic autoantibodies may be helpful in establishing the diagnosis (6).

The idiopathic form of subglottic stenosis is characterized histologically by dense fibrosis of the keloidal type separated by sparse fibroblasts (5). Chronic inflammatory cells are modest or even lacking and mucoserous glands and ducts are dilated. Calcification is absent. The surface epithelium generally shows squamous metaplasia or even ulceration with replacement by granulation tissue. The underlying cartilage typically shows little, if any, changes.

D. Treatment and Prognosis

Effective treatment depends on identifying and eliminating the cause and establishing an adequate airway. The latter may be achieved by endoscopic or laser excision of the stenotic airway, temporary tracheotomy, or segmental resection. Local recurrences, however, are not uncommon in the idiopathic variety.

V. TRACHEOPATHIA OSTEOCHONDROPLASTICA

A. Introduction

Tracheopathia osteochondroplastica (TPO) is an idiopathic disorder in which multiple ossified and/or cartilaginous nodules appear submucosally in the trachea, infrequently in the major bronchi, and exceptionally in the larynx (1–11). Fortunately, it is a rare condition. Jepsen and Sorensen observed 5 cases in 3500 bronchoscopies, while Prakash et al. identified only 1 in 2000 bronchoscopies (6,12). Eimind, on the other hand found no examples among 25,000 bronchoscopies (13).

B. Clinical Features

Although TPO has been observed in an 11-year-old girl, the vast majority of patients are over 50 years of age at diagnosis. The gender distribution depends on the study, some indicating either a male or female predominance (1,3). When viewed collectively, the gender distribution is probably about equal (7).

TPO typically involves the cartilaginous framework (anterior and lateral walls) of the lower two-thirds of the trachea. The posterior noncartilaginous membranous wall is not affected. The osteocartilaginous nodules are usually confined to the trachea but, on occasion, may involve the main stem bronchi. The segmented bronchi as well as the larynx are seldom affected.

Symptoms, which are often confused with asthma or bronchitis, vary with the degree of airway compromise. Some patients are asymptomatic while others experience chronic cough, hoarseness, wheezing, dyspnea, or repeated episodes of infections. Hemoptysis is not common.

A single case of familial TPO (mother and daughter) has been described (6). Serum calcium and phosphorous levels are normal (1).

C. Imaging

Imaging studies show multiple broad-based, symmetric, or asymmetric protrusions, often calcified with a beaded-scalloped appearance involving the anterior and lateral walls (3,5). The posterior (membranous) wall is spared. The nodules are covered with mucosa and centered in the submucosa attached to the cartilaginous framework.

D. Pathology

The nodules are composed of cartilage and/or bone, often with focal calcification, resembling small chondromas, exostoses, or osteochondromas. Some may even contain marrow spaces with hematopoietic elements (2). The nodules are centered in the submucosa and often maintain a continuity with the inner surface of the tracheal cartilage. The overlying mucosa is usually intact and may appear normal or metaplastic.

E. Treatment and Prognosis

There is no medical therapy for TPO. Asymptomatic patients require no treatment other than instructions to avoid respiratory irritants. Symptomatic patients, in turn, will usually have to have one or more of the nodules removed with meticulous attention to the long-term tracheobronchial hygiene to thwart off superimposed infections.

VI. CYSTS AND LARYNGOCELES

A. Introduction

Large saccules, some laryngeal cysts, and laryngoceles represent a spectrum of congenital and acquired disorders that occur within the saccular appendage of the laryngeal ventricle. To appreciate the clinical and pathologic features of these lesions, one must first consider the anatomy of this structure.

B. Anatomy and Terminology

The saccule, also known as the appendix of the laryngeal ventricle, is a blind respiratory epithelial-lined sac, which ascends vertically from the anterior one-third of the ventricle between the false cord and inner surface of the thyroid cartilage (Fig. 13). In infants, it is relatively large and lined by a papillary mucous membrane associated with subepithelial lymphoid aggregates (1). In adults, the mucosa is less complex and usually devoid of a lymphoid component. Approximately 60 to 70 mucous glands empty their secretions into the saccule, which in turn drains into the larynx. The saccular orifice at the ventricle measures only 0.5 to 1.0 mm and can therefore be easily compromised by atresia, tumors, infections, fibrosis, and trauma. The saccule is of variable depth but tends to be larger in males than females. Broyles observed that in 75% of the cases the saccule extended to a depth of 6 to 8 mm (2). In 25%, the depth extended

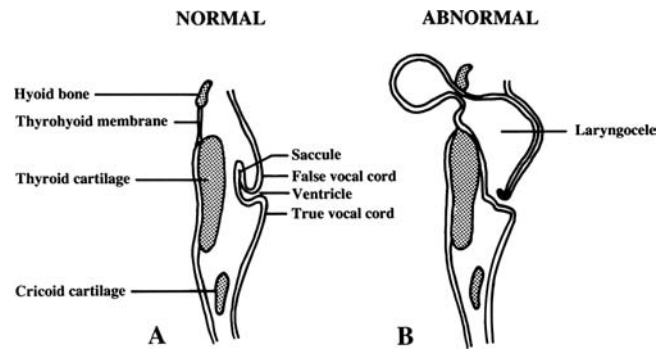


Figure 13. Diagram of a coronal section through the larynx at the level of the saccule demonstrating (A) normal anatomy and (B) a mixed laryngocele herniating through the thyrohyoid membrane.

10 millimeters or more and in 7%, the saccule extended 15 mm or more. Since the superior margin of the thyroid cartilage is approximately 16 mm above the superior surface of the vocal cords; this means that a small number of adults have saccules that extend above the cartilage (3). In the fetus and newborn, 25% of the saccules routinely extend beyond this border (4). These extended saccules are referred to clinically as “elongated saccules.” Apparently in some “normal” larynges, the saccule may be entirely absent (4). Although it may be a vestigial remnant of the ventricular air sacs of anthropoid apes, the saccule in humans appears to function as a source of lubricant for the vocal cords.

If the saccule becomes obstructed, secretions accumulate and a cyst is formed—the so-called saccular cyst (Fig. 14). If the saccule becomes distended with air and maintains an open communication with the laryngeal lumen, it is termed a laryngocele (Fig. 15).

C. Cysts

Cysts of the larynx can be classified as congenital or acquired; ductal or saccular; or as “tonsillar,” epithelial, or oncocytic (5–7). Most are acquired and of the ductal-epithelial type. They occur in all age groups but are most frequent in individuals over the age of 50 years (3,5–15). Although some studies have shown a male or female predominance, there is no gender preference when these studies are viewed collectively (3,6,7,12,14). Hoarseness, respiratory compromise, dysphagia, coughing, feeding problems, foreign body sensation in the throat, neck mass, and pain are common complaints. In many instances, the cysts are asymptomatic and represent only an incidental finding.

Cysts, which may be either solitary or multiple, occur primarily in the supraglottic larynx, less frequently in the glottis, and infrequently in the subglottis. They arise from obstruction of the ducts of mucous glands or the orifice of the laryngeal saccule.



Figure 14. Incidental saccular cyst (arrow) discovered in a larynx removed for squamous cell carcinoma. The cyst was lined by oncocytic epithelium and exhibited papillary infoldings. Such cysts are occasionally referred to as oncocytic papillary cystadenomas.



Figure 15. Gross picture of a resected external (air-filled) laryngocele that presented as a cyst of the neck.

Some cysts, particularly those of the subglottis, are clearly related to postintubation while at least some vocal cord cysts may be related to vocal abuse trauma (9,11,13).

In some studies, 20% to 30% of laryngeal cysts in infants and children, especially those of the saccular type, have been associated with a variety of congenital or developmental abnormalities (3,12,14). Among these are included Down's syndrome, cystic fibrosis, cerebral palsy, cardiac anomalies, prematurity, hydrocephalus, microcephalus, high arched palate, micrognathia, conductive hearing loss, laryngomalacia, and vocal cord paralysis.

One of the more popular classifications of laryngeal cysts has been that proposed by DeSanto et al. (5). These authors divide laryngeal cysts into two categories: (i) *ductal*, which represent about 75% of all cysts of the larynx and (ii) *saccular*, which comprise the remaining 25%.

Ductal Cyst

Ductal cysts arise when the ducts of mucous glands are occluded; hence, they can occur at any site where these glands are found. They are almost invariably less than 1 cm in diameter and are quite superficial, often appearing to arise within the mucosa. Forty percent occur in the vicinity of the true cords (excluding the free margin which is essentially devoid of glands), 37% in the epiglottis, 7% in the false vocal cords, 6% in the ventricles, 5% in the aryepiglottic folds, 3% in the arytenoids, and the remainder in the anterior commissure, pyriform sinus, and subglottis (5).

Saccular Cyst

Saccular cysts are mucous filled cysts that develop following obstruction of the laryngeal saccule. They are always of supraglottic origin, distinctly submucosal, covered by a normal mucous membrane, and vary from 1 to 7.5 cm in diameter (Fig. 14). They most often present in the region of the ventricles (58%), aryepiglottic folds (14%), lateral larynx (12%), or involve a combination of adjacent sites (5).

There are two types of saccular cysts—anterior and lateral. Approximately 60% of saccular cysts are anterior (3,5). They arise near the orifice of the ventricle and overhang the anterior glottis. Lateral saccular cysts, on the other hand, tend to bulge the aryepiglottic folds, false vocal cords, or epiglottis and, in a few instances, may extend through the thyrohyoid membrane to present in the neck. Whether a given cyst is classified as anterior or lateral depends on the length of the saccule and the level of obstruction.

Histologically, ductal and saccular cysts are both lined by respiratory or squamous epithelium and, therefore, have no distinguishing characteristics. A few may even be lined, either focally or entirely, by oncocytic epithelium. Accordingly, the DeSanto classification of laryngeal cysts into ductal or saccular is largely clinical based on location, depth, and size and is difficult for pathologists to use, and especially so, since some of these cysts are removed in pieces destroying the relation of the cyst to the surface mucosa. This has caused pathologists to search for a more useful but clinically relevant classification. That proposed by Newman et al. seems to fill this void (6)

Table 1 Classification of Laryngeal Cysts

I. Tonsillar cysts
II. Epithelial cyst
A. Ductal
B. Saccular
i. Anterior
ii. Lateral
III. Oncocytic cyst (oncocytic papillary cystadenoma)

(Table 1). They propose three categories of laryngeal cysts: tonsillar, epithelial, and oncocytic. In a collective review of 92 patients with laryngeal cysts classified according to the scheme of Neuman et al., 61% had epithelial cysts, 25% tonsillar cysts, and 14% oncocytic cysts (6,7).

Tonsillar Cyst

Tonsillar cysts resemble a palatine tonsillar crypt distended with keratin, hence the name. They occur almost exclusively in the epiglottis, vallecula, or pyriform sinus and may be single or multiple. They are usually small and are lined by stratified squamous epithelium, filled with keratin, and surrounded by lymphoid tissue with prominent germinal centers (Fig. 16).

Epithelial Cyst

These cysts are also found primarily in the supra-glottic larynx, pyriform sinus, or vallecula. They may

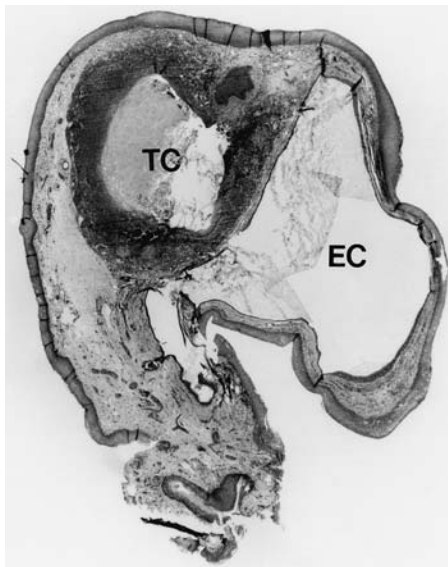


Figure 16. A 42-year-old man presented with a sensation of a “foreign body in his throat.” Endoscopic examination revealed a cyst of the left pyriform sinus. Microscopically, the specimen consisted of two adjacent cysts: (i) a tonsillar cyst (TC) filled with keratin, lined by stratified squamous epithelium and surrounded by lymphoid tissue; and (ii) an epithelial cyst (EC) also filled with keratin and lined by stratified squamous epithelium, but without a mantle of lymphoid tissue (H&E, 20×).

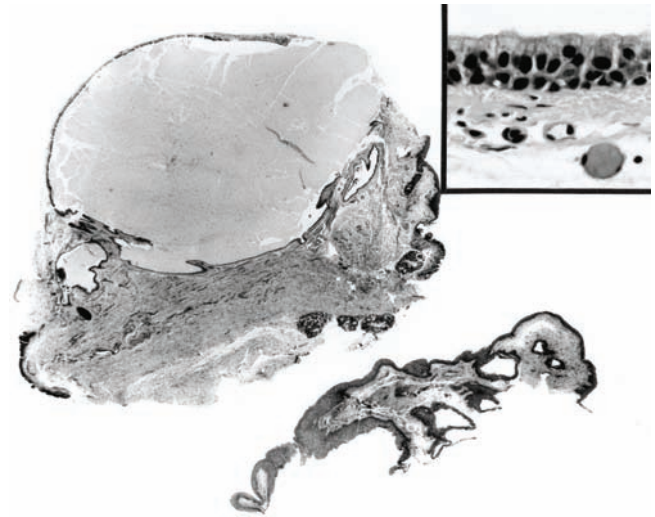


Figure 17. Epithelial cyst filled with mucin and lined by attenuated respiratory epithelium (H&E, 20×; insert, 300×).

or may not have papillary infoldings and are lined entirely by respiratory epithelium, squamous epithelium, or both or by a nonspecific attenuated epithelium. They may therefore contain either keratin or mucin (Figs. 16 and 17). Some are focally associated with small aggregates of lymphoid tissue. With additional clinical information, these cysts can be further subdivided into ductal and saccular (anterior or lateral). See previous discussion on ductal and saccular cysts.

Oncocytic Cyst

These cysts occur primarily in the area of the false cords and ventricles in patients over the age of 50 years. They may be either unilocular or exhibit papillary infoldings. Those exhibiting the latter feature are also referred to as oncocytic papillary cystadenomas. The cardinal features of these cysts are their oncocytic epithelium and their tendency, on occasion, for multifocality and local recurrence (Fig. 18).

Treatment

In order to avoid laryngeal stenosis, cysts in infants and children should be managed conservatively. Some advocate needle aspiration initially. Recurrence may necessitate repeat aspiration, or, in some instances, the cyst may have to be deroofed, removed with cup forceps, or marsupialized with lasers (16). Small cysts in adults can be treated similarly. Larger cysts often require excision externally.

Laryngocoele

Laryngocoeles are abnormal dilatations of the saccule. They differ from saccular cysts in that they contain air rather than mucus and maintain an open communication with the lumen of the larynx (Figs. 13B, 15, and 19). The distinction between a long saccule and a

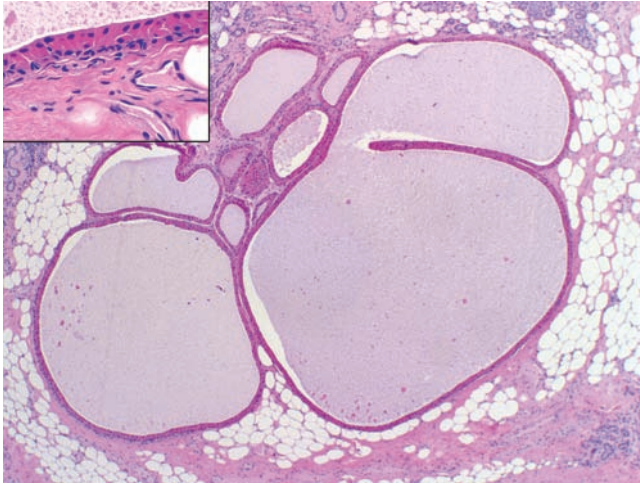


Figure 18. Oncocytic cyst. Note the focal intracystic papillary projection and oncocytic character of the epithelium (*insert*). Such cysts are often referred to as oncocytic papillary cystadenomas (H&E, 40 $\times$; insert, 200 $\times$)

laryngocele is somewhat subjective. According to Holinger et al., a long, ectatic saccule becomes a laryngocele when it is (i) symptomatic, (ii) palpable, (iii) observed internally by indirect or direct laryngoscopy, and (iv) observed radiologically or by dissection to extend above the superior margin of the thyroid cartilage (3). About 2% of "normal" larynges harbor laryngoceles (17).

Laryngoceles are more common in the 40- to 70-year age group and are seven times more frequent in men than women (18). They are subclassified into three categories—internal, external, and mixed. They are termed "internal" when confined to the intrinsic larynx, "external" when present in the neck communicating with an undistended saccule through the thyrohyoid membrane, and "mixed" when both are present (Fig. 19). The reported incidence of each is variable. Canalis reviewed 131 cases and observed 44% to be mixed, 30% internal, and 26% external (18). Macfie evaluated 52 patients, classifying 69% as mixed and 31% internal (19). About 20% to 35% of laryngoceles are bilateral.

Patients with symptomatic internal laryngoceles usually present with hoarseness or change in quality of the voice, dyspnea, cough, or sensation of a mass in their throat. External laryngoceles manifest as a soft reducible neck mass accentuated by an increase in intralaryngeal pressure or as subcutaneous emphysema (20,21). Laryngoceles can become infected (laryngopyocele) following upper respiratory infections or the use of diagnostic procedures (Fig. 20).

Laryngoceles may be congenital or acquired (22). They are usually associated with increased intralaryngeal pressure and, consequently, are common occupational hazards among glass blowers, musicians who play wind instruments, and weight lifters (19).

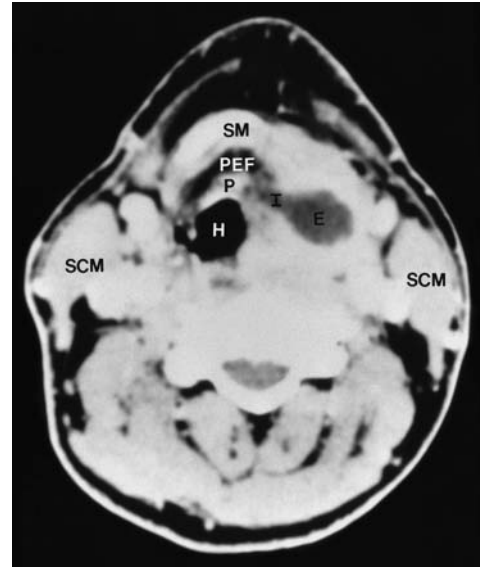


Figure 19. Computer tomography scan showing a mixed laryngocele with large external (E) and small internal (I) components. *Abbreviations:* SM, strap muscles; P, petiole; H, hypopharynx; PEF, pre-epiglottic fat; SCM, sternocleidomastoid muscle. *Source:* Image Courtesy of Dr. Jane Weissman, formerly of Pittsburgh, PA.

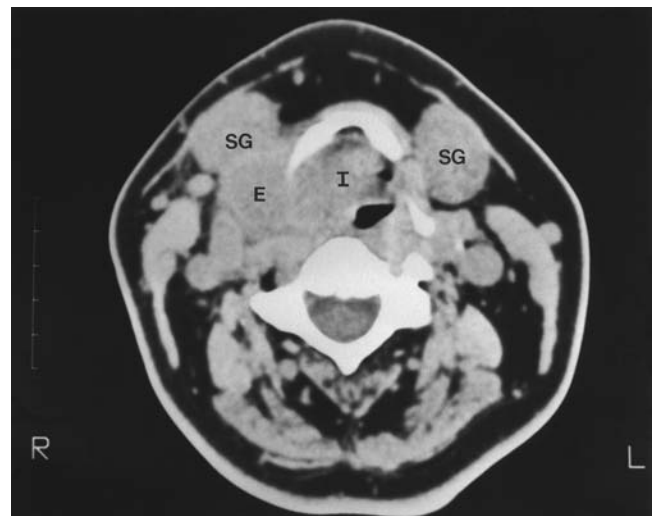


Figure 20. Computed tomography scan showing an infected mixed laryngocele (laryngopyocele). Both external (E) and internal (I) components are filled with dense secretions (compare with air-filled laryngocele in Fig. 15). *Abbreviation:* SG, submandibular gland. *Source:* Image courtesy of Dr. Hugh Curtin, Boston, MA.

Carcinoma of the larynx is sometimes associated with a laryngocele (Fig. 21). The frequency of this association varies according to the stringency of criteria used for diagnosing a laryngocele (elongated

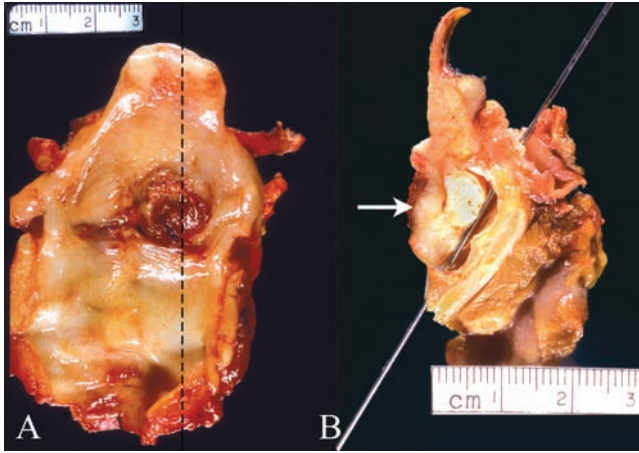


Figure 21. (A) Squamous cell carcinoma of the supraglottic larynx associated with a laryngocele. The larynx was sectioned vertically (*hash marks*) to show their relation. (B) Cross section of tumor shown in A. Probe passes through the laryngocele. Note tumor (*arrow*) compressing the orifice of the saccule.

saccule vs. laryngocele) and whether or not the findings are based on anatomic or radiographic studies. The literature indicates that somewhere between 0% and 29% of all laryngeal carcinomas are associated with laryngoceles (17,23–26). Conversely, of all laryngoceles, 15% to 49% are associated with carcinoma (21,24). Generally, the carcinoma is clinically obvious, but in a few instances (4%), the lesion will present initially as a laryngocele with an occult carcinoma (24). The carcinoma may be etiologically related to the laryngocele by acting as a ball-valve mechanism entrapping air in the saccule. In some cases, however, the carcinoma is on the side opposite the laryngocele. In this instance, it has been speculated that the tumor activates the cough reflex causing an increase in intralaryngeal pressure with dilatation of the saccule. Most (74%) cancer-associated laryngoceles are of the internal type (24).

Asymptomatic laryngoceles require no treatment but in the adult, direct laryngoscopy and biopsy are mandatory in order to rule out concomitant carcinoma. When symptomatic and large, they may have to be excised through an external approach (Fig. 15). Laryngopyoceles are best treated by incision and drainage, antibiotics, and removal after the infection has subsided.

VII. PAPILLOMAS

A. Introduction

Papillomas are the most common benign tumor of the larynx (1). They can be divided clinically into three categories according to age of onset (juvenile vs. adult), severity of disease (aggressive vs. nonaggressive), and number of lesions (solitary vs. multiple) and

histologically into nonkeratinized and keratinized types (2–9).

In general, nonkeratinized papillomas occur primarily in children and young to middle-aged adults, may be solitary or multiple, are etiologically related to the human papillomavirus (HPV) types 6 and 11, often stubbornly recur following excision, and have little malignant potential. In contrast, keratinized papillomas occur primarily in adults, are usually solitary lesions, generally are not related to a virus, may or may not recur, and occasionally have a malignant potential.

B. Recurrent Respiratory Papillomatosis—Nonkeratinized Papilloma

Terminology

Recurrent respiratory papillomatosis (RRP, papillomatosis, juvenile papillomatosis, laryngeal papillomatosis) is the term currently preferred to describe a “benign” disease of the aerodigestive tract characterized by the appearance of one or more, viral-related squamous papillomas that have a persistent tendency for recurrence and a relative resistance to treatment. Terms such as juvenile papillomatosis are inappropriate, since the disease may persist into adulthood or may not even manifest until late in life. Laryngeal papillomatosis is also inaccurate since the disease may involve other sites in the aerodigestive tract, including the oral cavity, trachea, and lungs.

Etiology

The long-presumed viral etiology of RRP has now been conclusively established. The disease is caused by the HPV, especially types 6 and 11, a DNA virus that belongs to the family *Papoviridae*. This was first suggested in 1923 when Ullman successfully transplanted a homogenate of a laryngeal papilloma removed from one of his patients to his own arm (10). More recently viral antigens or genomes have been demonstrated in laryngeal papillomas by immunohistochemistry, in situ hybridization, and the polymerase chain reaction (11–17). Viral particles consistent with HPV have also allegedly been identified by electron microscopy, although the frequency of finding these particles ultrastructurally has varied from 0% to 20% (18–22).

The female genital tract is the predominant viral reservoir from which the respiratory infection is acquired. Retrospective studies have shown that approximately 30% to 70% of patients with RRP are born to mothers with condylomata acuminata (genital warts which are also etiologically related to HPV 6 and 11) (20,21,23,24,25). Although condylomata acuminata are easily recognized, cervical flat warts (also related to HPV) are frequently overlooked or subclinical. It is therefore possible that women with cervical flat warts could transmit the virus to their newborns without knowledge of their infection (24). This could explain why the mothers of many individuals with RRP have no history of genital warts.

Kashima et al. indicate that patients with juvenile-onset RRP (JO-RRP) are frequently characterized by a clinical triad: (i) first born child, (ii) vaginal delivery, and (iii) a teen-aged mother (26). It is known that teen-aged mothers at the time of first delivery have prolonged labors, with subsequent increased exposure to the virus. In their study, 32% of patients with JO-RRP and none of those with adult-onset RRP (AO-RRP) manifested the complete triad. This compared with a 10% and 3% incidence, respectively, in a control population of normal juveniles and adults (26).

The risk of acquiring RRP in children born vaginally to an HPV-infected mother ranges from 1 in 143 deliveries for those with a history of condyloma during pregnancy to 1 in 400 deliveries for those women with an active or latent HPV infection as demonstrated by cervicovaginal swabs for the prevalence of HPV DNA (27–29). The low rate of RRP in exposed children suggests that additional factors (? immune) may be necessary before acquiring the disease. Nevertheless, there is an on-going debate with medicolegal overtones on whether a pregnant woman with known condylomas should be permitted to deliver vaginally or by elective cesarean section (30,31). Although cesarean sections do diminish the odds for acquiring RRP, the protection is not absolute, as illustrated in the study of Wiatrak et al. (32). These authors evaluated 73 patients with JO-RRP. The mode of delivery was known in 69, and of these, 64 (93%) were delivered vaginally and 5 (7%) by cesarean section.

In AO-RRP, risk factors are less conclusive. Conceivably such individuals may acquire the virus at the time of delivery. The virus may then remain dormant, only to express itself in adulthood. Oro-genital contact with an infected partner is also receiving increasing attention (21,26).

There is no known instance of RRP occurring among siblings or transmission of the disease attributed to therapeutic interventions in the newborn nursery (26). There is an interesting case report, however, of a surgeon who contacted the disease following laser therapy of some of his patients who had anogenital condylomas (33). It was speculated that he acquired the disease by inhaling viral particles present in the laser plume.

RRP is an uncommon disease. In the United States, it is estimated that approximately 2400 new cases among children and 3600 new cases among adults are diagnosed each year, with an incidence of about 1.7 to 4.3 per 100,000 children and 1.8 per 100,000 adults (28,29,32,34–38). Despite its rarity, the impact of the disease on patients, their families, and the health care system is immense. It is not unusual for some individuals to require more than 100 surgical procedures with an average lifetime cost of thousands of dollars.

Clinical Features

According to the age at initial diagnosis, RRP is commonly divided into two categories: JO-RRP and

AO-RRP. The age limit that defines these categories, however, is arbitrary and highly variable. For instance, JO-RRP has been defined in various studies as patients who present before the age of 12, 16, 18, or 20 years and AO-RRP as those who present over these ages (5,13,26,30). In a review of 110 cases of RRP, Strong et al. noted that 66% of patients experienced onset of the disease between birth and 15 years of age while 34% developed their disease at 16 years of age or later (21). The majority of patients with JO-RRP become symptomatic between two and five years of age. Abnormal crying, hoarseness, dyspnea, cough, dysphagia, and stridor are the usual symptoms.

The clinical course is, to some extent, correlated with the age of onset. In JO-RRP, the distribution between the two sexes is about equal and the papillomas are more often multiple (80–98% of all cases) and frequently exhibit extensive growth and occasionally rapid recurrence after excision (5,21,31). JO-RRP may remit spontaneously or persist into adulthood. AO-RRP, in contrast, is three to four times more common in males and the papillomas are multiple in only 25% to 35% of cases and recur less often (5,39).

The disease almost invariably involves the larynx, especially the true and false vocal cords and ventricles. In more advanced cases, the lesions may also involve other laryngeal sites, nasal cavity, lips, gingiva, palate, nasopharynx, esophagus, trachea, bronchi and/or lungs. Data derived from the National registry for JO-RRP ($N = 603$ children) indicate that in 87.4% of cases only one anatomic site is involved, while in 9.8%, 2.6%, and 0.2%, two, three, and four sites, respectively, are involved (35).

Extension of papillomas into the trachea or bronchi occurs in 2% to 15% of patients, an event that is usually associated with subglottic disease and prior tracheotomy (21,35,37,40–43). Some individuals (1–5%) may even have pulmonary parenchymal involvement (32,43–48). This is a potentially ominous finding as these individuals often die of their disease (43). Atelectasis, bronchiectasis, and thin-wall cavities with smooth borders are the most common roentgenographic signs of lung disease. Patients with bronchoalveolar involvement tend to follow a common pattern: (i) the majority have had laryngeal papillomas discovered before the age of five years, (ii) the interval between the onset of laryngeal disease and the discovery of bronchoalveolar papillomatosis averages 12 years (range 1–36), (iii) all have tracheostomies, and (iv) all have worn tracheal cannulas for extended periods of time (43).

The distribution or recurrence of papillomas in the aerodigestive tract, however, is not random, according to Kashima et al., but instead follows a predictable pattern with lesions occurring at sites in which ciliated respiratory and squamous epithelia are juxtaposed (squamociliary junction) (49). Injury to a ciliated mucosa such as from a biopsy or surgical procedure often results in squamous metaplasia, creating an iatrogenic squamociliary junction and predisposing the patient for additional lesions. This might explain the tendency for papillomas to occur at tracheostomy sites.

Pathology

Grossly the papillomas present as one or more, pink, soft, warty growths that are often confluent and bleed with minor trauma (Fig. 22). By light microscopy, they are composed of papillary fronds of squamous cells containing fibrovascular cores (Fig. 23). Although typically nonkeratinized, an occasional case may show a very thin scale of surface orthokeratin or parakeratin (Fig. 24). The stroma is well vascularized and may or may not contain inflammatory cells. Intranuclear or intracytoplasmic viral inclusions are not seen but koilocytic changes may be observed in some instances. According to Lack et al., 48% of unselected papillomas will be positive for HPV on immunostain-

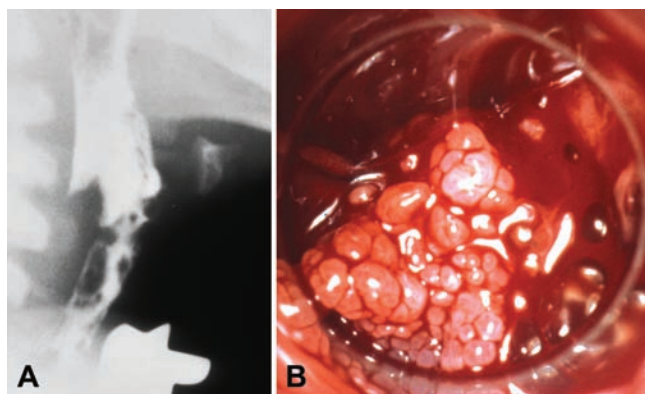


Figure 22. Recurrent respiratory papillomatosis. (A) Laryngo-gram demonstrating multiple filling defects of the larynx. Note the tracheal canula. (B) Laryngoscopic view showing multiple, friable, occasionally confluent papillary growths. *Source:* Images courtesy of Dr. Mark May, (retd.) Shadyside Hospital, Pittsburgh, PA.

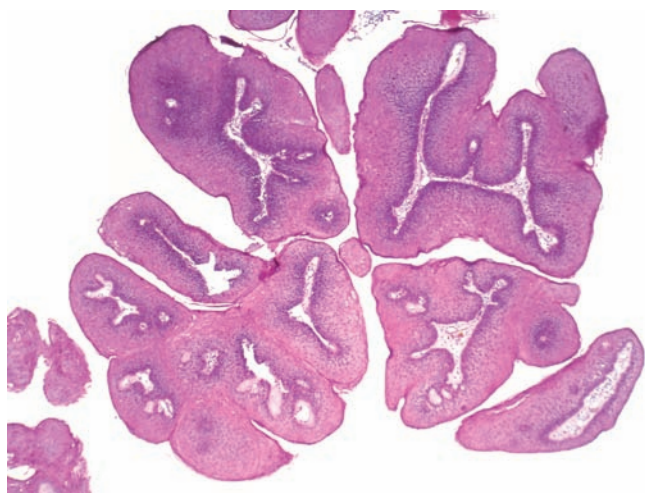


Figure 23. Low-power view of a squamous papilloma associated with recurrent respiratory papillomatosis (H&E, 20 $\times$).

ing (11) (Fig. 25). In a review of 58 cases of JO-RRP in which the virus was genotyped at the time of initial therapy, Wiatrak et al. observed that in 53.5% of cases the virus was HPV 6, in 39.7% HPV 11, and in 6.9% both HPV 6 and 11 were found (32). Similarly, in a study of 24 AO-RRP in which the papilloma was genotyped, Pou et al. observed 87.5% were HPV 6, 8.3% HPV 11, and 0.04% HPV 16 (50). Interestingly, they also found coinfection with other viruses. In 12 cases (50%), *Herpes simplex* was found and in 3 cases (12.5%) Epstein-Barr was observed. None were associated with cytomegalovirus. They raised the possibility that viral coinfection might be predictive of an aggressive clinical course.

The histologic appearance of the papillomas tends to reflect the clinical activity of the disease (51,52). Papillomas that recur within one month of

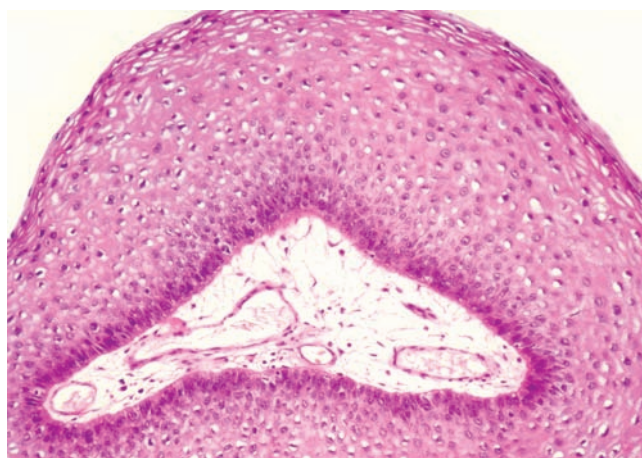


Figure 24. The typical squamous papilloma of recurrent respiratory papillomatosis demonstrates orderly growth and maturation of the epithelial cells. There is little, if any, tendency to keratinize.

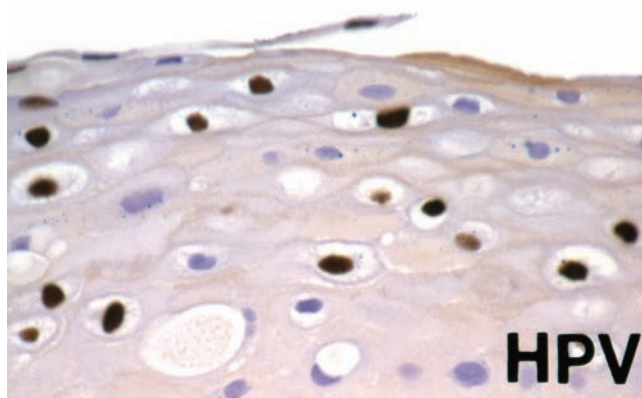


Figure 25. Squamous papilloma of recurrent respiratory papillomatosis positive for human papillomavirus (immunoperoxidase, 40 $\times$).

excision frequently display varying degrees of atypia manifested by basal cell hyperplasia, increased mitotic rate, prominent nucleoli, and focal variation in nuclear size and shape. As the activity of the disease lessens, the papillomas tend to revert back to normal epithelial maturation.

Immunohistochemistry

Basal and occasionally suprabasal cells of papillomas associated with RRP often stain positive by immunohistochemistry for Ki-67 and p53 (53–57). The significance of these findings is controversial. Some indicate that these markers, especially if found throughout the epithelium, correlate with more frequent recurrence and possible malignant transformation while others contend that they have no predictive value.

Lele et al. examined four cases of HPV-11 JO-RRP progressing to carcinomas utilizing immunostains for p53, pRb, p21, and p16 (58). They observed a marked increase expression of p53 and pRb and a simultaneous decrease in p21 as the lesion progressed from benign to dysplastic to malignant. p16 was expressed in all lesions and was, therefore nondiscriminatory. On the basis of this combination of stains, the authors suggested that lesions with a malignant potential could be recognized. In contrast, Xu et al. studied a single case of HPV-11 AO-RRP that progressed to carcinoma in which these stains (p53, Rb, and p16) were applied (59). They found these stains to be unaltered during tumor progression.

Molecular-Genetic Data

Patients with RRP may be unable to resist or control their disease because of an ineffective HPV-specific T-cell response. Bonagura et al. have observed that these individuals have an elevated percentage of CD8-positive, CD28-negative T-cells, and that the T-cells often express an increase in TH2-like cytokine mRNA in response to autologous papilloma tissue (60). These patients, otherwise, are not prone to other nonviral infectious agents.

Human leukocytes antigens (HLA) may also be important in the etiopathogenesis of the disease. Gelder et al. studied a cohort of 60 RRP patients in the United Kingdom for HLAs and compared the results to 554 controls (61). Of these 60 patients, 36 had JO-RRP and 24 AO-RRP. They noted that HLA DRB1*0301 was disproportionately present in the RRP patients (55%) compared with the control population (25%). The possibility of a genetic association between this HLA and susceptibility was raised. Bonagura has also observed a potential relationship between HLA DQ3 and DR11 and RRP (62).

More recently, Rahbar, et al. found that vascular endothelial growth factor—A (VEGF-A) was strongly expressed in the squamous epithelium of the papillomas and that VEGF receptors 1 and 2 were strongly expressed in the endothelial cells of the underlying blood vessel (63). Neither strong labeling of VEGF-A nor labeling of its receptors was noted in the control population, suggesting that these factors may be

important in pathogenesis of the disease. If so, anti-vascular therapy may be of therapeutic value.

Treatment and Prognosis

The natural history of RRP is highly variable and unpredictable with remissions and exacerbations occurring for no apparent reason. Some patients have only one or two papillomas with local recurrence every two or three years and eventual spontaneous remission while others have extensive life-threatening disease. Benjamin and Parsons describe a patient who had 20 operative procedures for JO-RRP and then remained disease-free for 25 years, only to experience another nine operations for recurrent disease later in life (4). During periods of active growth, papillomas may appear every two to four weeks, and it is not uncommon for some patients to have undergone 50 to 100 operations or more for removal.

Majoros et al. followed 65 children and observed that the disease lasted five years or more in 80% (42). Ruparelia et al. identified 165 cases of JO-RRP with a median follow-up of 1.7 years (range 0.01–4.61 years). Disease remission, defined as the absence of surgical intervention for at least one year, was seen in 36 (21.8%) of the children (64). It would appear, however, from the case of Benjamin and Parsons noted above, that patients with RRP may be at risk for possible local recurrence throughout their life span (4).

The effect of puberty on the course of the disease is controversial. Some are of the opinion that papillomas become less aggressive or even disappear during puberty while others contend that puberty has no relationship to the outcome of disease (4,21,42,65–67). The effect of pregnancy is also controversial; in some pregnant women, the disease may resolve while in others it may become more aggressive (25,39,65).

Although there are no parameters that allow one to predict the course RRP, it is generally agreed that individuals who experience the onset of disease prior to three years of age, have more than one anatomic site of involvement, and are infected with HPV-11 tend to have a more aggressive disease.

Since RRP is often characterized by periods of active growth and remission, it is difficult to evaluate the efficacy of various therapeutic modalities. According to Strong et al., there are three goals of management: (i) to maintain the airway and voice and to avoid tracheotomy whenever possible, (ii) to reduce the tumor burden to minimal proportions in hopes of achieving remission via host responses, and (iii) in the presence of tracheotomy maintain the patency of the airway by bronchoscopy and to use the shortest possible tracheotomy tube (21). Tracheotomy, however, is ultimately required in a 1.8% to 64% of all patients with RRP, with an average incidence of 30% in combined studies (68,69).

The current standard treatment is microlaryngeal surgery using forceps, the microdebrider, or CO₂ laser. Complications of treatment include webs, fibrosis, arytenoid fixation, and laryngeal stenosis (70). In general, the more vigorous the therapy, the greater the complications.

Surgical excision of the papillomas, however, is only a palliative procedure. It has been shown for instance, that HPV can be found by DNA hybridization or the polymerase chain reaction in the adjacent or nearby nondiseased mucosa in approximately 40% to 75% of patients. The persistence of the virus explains the tendency for recurrence (17,71–73). As a result, search for effective adjuvant medical therapy is ongoing (37,74,75).

The overall mortality rate in patients with RRP has varied from 4% to 14% (42,65,76). Causes of death have included asphyxia, infections, pulmonary complications, and superimposed carcinoma.

Carcinoma complicating RRP, so-called carcinoma ex papilloma, is an infrequent occurrence (77–92). In some instances, the carcinoma occurs “spontaneously” while in others, it seems to be related to prior radiation exposure. Some patients with RRP are also heavy smokers or consumers of alcohol, which may act as additional co-carcinogens or promoters in the development of carcinoma.

The incidence of carcinoma developing in the nonirradiated patient is stated to be 2% and for the irradiated patient, 14% (3,4,85). According to Lindenberg and Elbrond, there is a 16-fold increased risk of a subsequent carcinoma in patients who have received irradiation for their RRP (84). Even a small dose of irradiation may be carcinogenic in these patients.

Carcinoma complicating RRP develops in either the larynx or lung, and prognosis depends, to a large extent, on whether the tumor arises spontaneously or follows radiation exposure. Kashima et al. reviewed 17 patients with RRP who developed laryngeal carcinoma (81). Of the seven patients who developed spontaneous laryngeal carcinoma, all had JO-RRP. The average interval from onset of RRP to the development of carcinoma was about 30 years, but only one of six patients available for follow-up died of disease. In contrast, of the 10 patients that developed laryngeal carcinoma following irradiation, 9 had JO-RRP with the average interval from onset of RRP to the occurrence of the carcinoma of about 10 years. Eight of the 10 patients with follow-up died of disease.

Guillou et al. reviewed 14 cases of spontaneous squamous cell carcinoma of the lung that occurred in nonsmoking, nonirradiated patients with RRP and observed the following characteristic profile: (i) all patients developed laryngeal papillomatosis around 2.5 years of age (range 1–6 years), (ii) lung carcinoma was diagnosed at about 15 years after the onset of laryngeal papillomatosis (range 4–26 years), (iii) all patients presented with pulmonary extension of their papillomatosis, (iv) the tumor was usually a well to moderately differentiated squamous cell carcinoma often with regional lymph nodes and distant metastases, and (v) most patients died soon after diagnosis of the carcinoma (82).

In most cases in which the papilloma and carcinoma have been examined for HPV, each has contained HPV-11. Rarely, HPV-6, 16, or 18 have been identified.

The squamous carcinomas are generally well differentiated and, at times, difficult to distinguish

from a papilloma. Some authors have also observed that the transformation of RRP to squamous cell carcinoma does not always progress through the usual dysplasia sequence (60).

Crissman et al. studied by image analysis the DNA content of papillomas obtained from seven patients with RRP (5 JO-RRP and 2 AO-RRP) (93). All of the papillomas microscopically exhibited areas of atypia/dysplasia and, when these foci were specifically examined, six of the seven were found to have abnormal (aneuploid) DNA. The significance of this finding, however, is uncertain since none of the six individuals developed carcinoma after an average follow-up of 30 years.

C. Keratinized Papilloma—Papillary Keratosis

Keratinized papillomas, as previously indicated, occur primarily in adults; are usually solitary lesions; generally are not related to a virus; may be etiologically linked, in some instances, to smoking; may or may not recur; and occasionally exhibit malignant potential (8,9,12,94–96). The majority arises from the true vocal cord and manifest clinically as hoarseness.

It has been our experience over the years that many clinicians and pathologists do not appreciate the differences between keratinized and nonkeratinized papillomas and equate the term “papilloma,” regardless of histologic appearance, as being of viral origin and akin to recurrent respiratory papillomatosis. To avoid this misunderstanding, we advocate the use of the term “papillary keratosis” in place of “keratinized papilloma.”

Papillary keratoses rarely exceed two cm. and are composed, histologically, of fronds of squamous cells with fibrovascular cores covered by a thick scale of orthokeratin or parakeratin (Figs. 26 and 27). In some cases, the papillary fronds are small but yet there is a definite papillary configuration to the surface epithelium. Keratohyalin granules are usually, but not invariably, present, and the stroma contains sparse to absent inflammatory cells. Not infrequently, the squamous component will exhibit varying degrees of dysplasia which, if observed, should be quantitated as mild, moderate, or severe, e.g. papillary keratosis with moderate dysplasia (Figs. 28 and 29). Likewise, if no epithelial disturbances are seen, it too should be noted, e.g., papillary keratosis without dysplasia.

Clinically, the papillary keratoses appear to have the same significance as the flat keratoses. See “Section X” below.

Papillary keratosis may be confused, both clinically and microscopically, with verrucous carcinoma (VC) of the larynx (97,98). Verrucous carcinoma, however, contains expanded, club-shaped rete pegs, often distended with keratin, and a markedly inflamed stroma. Papillary keratosis, in contrast, has thin, pointy rete pegs and, at most, only a mildly inflamed stroma. In addition, papillary keratosis usually, but not invariably, has rather uniform keratohyalin granules in the epithelial cells just beneath the keratin layer (stratum granulosum). These granules are characteristically

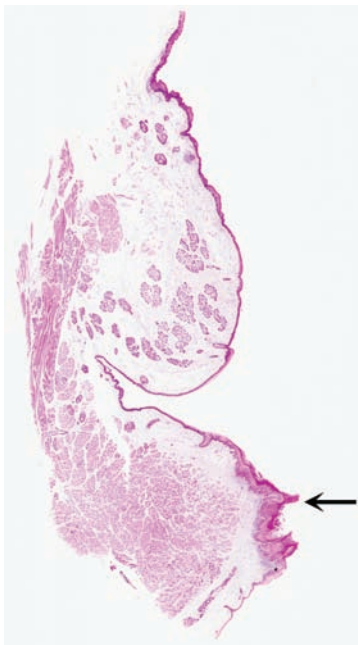


Figure 26. Papillary keratosis without dysplasia of right true vocal cord (arrow; H&E, whole mount).

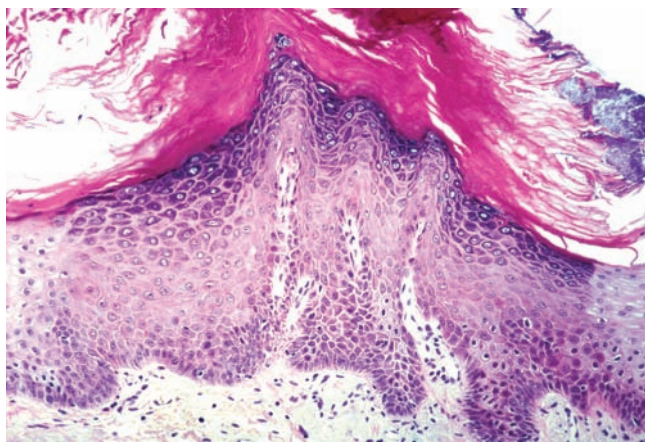


Figure 27. Papillary keratosis (keratinized papilloma shown in Fig. 26). Note the papillary, heavily keratinized surface, prominent keratohyaline granules, and absence of dysplasia (H&E, 140×).

sparse to absent in verrucous carcinoma. The presence of more than just “inflammatory atypia/dysplasia” supports the diagnosis of papillary keratosis rather than verrucous carcinoma. Verrucous carcinoma of the larynx is also uncommon below the age of 50 years and often exceeds 2 cm in size, whereas papillary keratosis is not infrequent below the age of 50 and rarely exceeds 2 cm.

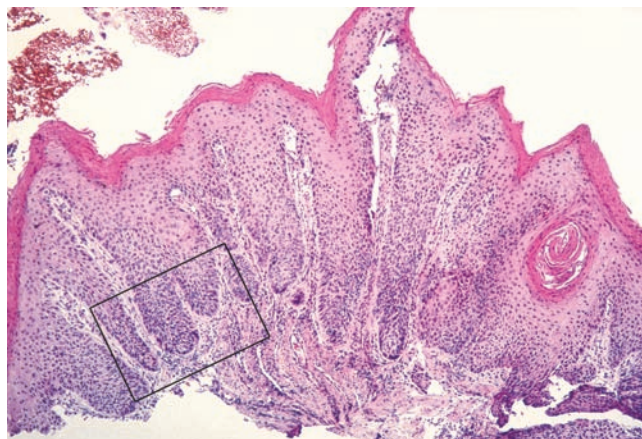


Figure 28. Papillary keratosis with mild to moderate epithelial dysplasia. Note the papillary and heavily keratinized surface. Keratohyaline granules are, however, absent (H&E, 100×) (see Fig. 25).

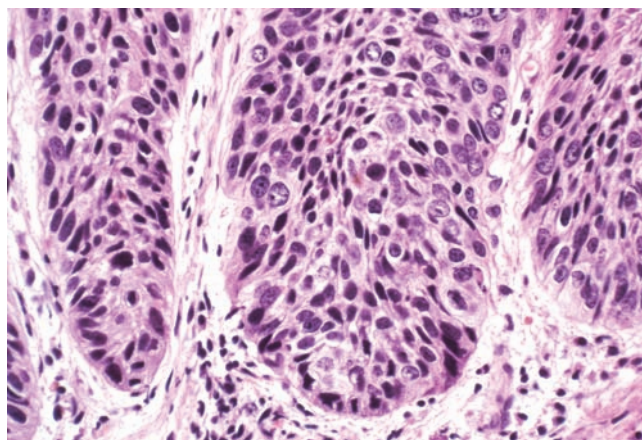


Figure 29. Higher magnification of the boxed area shown in Figure 28. Note the dysplasia (H&E, 400×).

VIII. VERRUCA VULGARIS

A. Introduction

Verruca vulgaris occurs primarily on the skin and is etiologically related to the HPV. On occasions, it can also arise on mucous membranes, particularly the lips, infrequently in the oral cavity, and exceptionally in the larynx (1–6). In the latter location, it may be confused with papillary keratosis, condyloma acuminatum, and verrucous carcinoma.

B. Clinical Features

Barnes et al. described one case and reviewed seven additional cases of verruca vulgaris of the larynx

(VVL) reported in the English language literature (2,6). These eight patients, seven men and one woman, were aged between 37 and 70 years (average 58 years). Although not always indicated, the true vocal cord appeared to be the most common site of origin and hoarseness the predominant symptom.

Most presented as unilateral, sometimes bilateral, exophytic sharply demarcated white growths, usually between 0.3 and 0.7 cm. In one case, however, the lesion involved almost the entire length of the vocal cord (2).

C. Pathology

Histologically, VVL resembles its cutaneous counterpart in all respects (Figs. 30 and 31). Most will also be positive, on immunostaining, for HPV. Virologically, however, there does appear to be a difference. Using in situ hybridization, Barnes et al. studied a single case of VVL and found it to contain HPV 6 or 11 which was unexpected because verruca vulgaris of the skin, lips, and oral cavity is associated with HPV 2 and 4 (3,5,6). This implies that verruca vulgaris can be caused by HPV types other than 2 and 4. In addition, since HPV 6 and 11 are the same genotypes associated with recurrent respiratory papillomatosis (laryngeal papillomatosis), it further indicated that VVL is at least virologically more related to recurrent respiratory papillomatosis of the larynx than to its counterpart on the skin, lips, and oral cavity.

D. Differential Diagnosis

VVL should be distinguished from “ordinary” papillary keratosis (keratinized papilloma), condyloma acuminatum, and verrucous carcinoma. Both VVL and papillary keratosis occur in adults and involve the true vocal cords. Both are heavily keratinized and

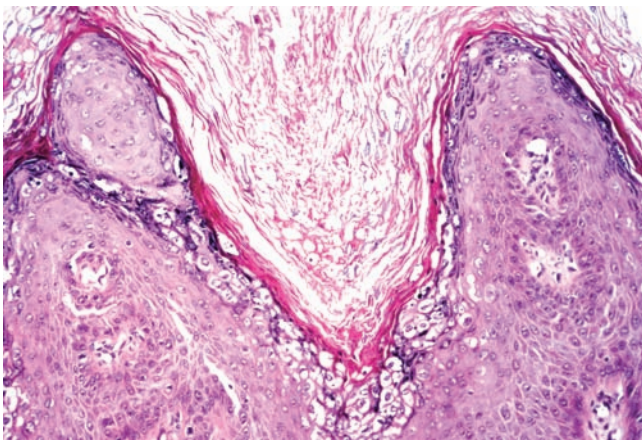


Figure 30. Verruca vulgaris of the true vocal cord showing marked acanthosis, papillomatosis, keratosis, prominent keratohyaline granules, and koilocytes (H&E, 200 $\times$). *Source:* From Sec. VIII, Ref. 6)

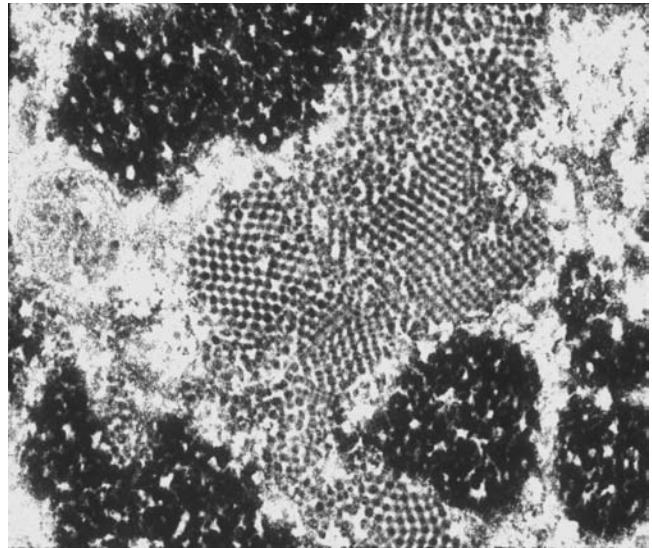


Figure 31. Electron microscopy of verruca vulgaris of the true vocal cord in Figure 30 showing intranuclear viral particles consistent with the human papillomavirus.

contain prominent keratohyalin granules. However, in contrast to VVL, papillary keratosis lacks clear cells in the epithelial layer (koilocytes) and is almost invariably negative on immunostaining for HPV. Moreover, papillary keratosis often exhibits varying degrees of dysplasia, which is not seen in VVL.

Condyloma acuminatum and VVL share many histologic features and the differences between the two are more quantitative than qualitative (7–9). In general, VVL is more heavily keratinized than condyloma acuminatum and contains larger and more variably sized keratohyalin granules. The rete pegs in VVL also tend to be more pointed and elongated.

Like VVL, VC of the larynx occurs in adults (median age 58 years) exhibits a male predominance, arises primarily from the true vocal cords, and is heavily keratinized (10). VVL can be separated from VC by the presence of numerous large keratohyalin granules and prominent koilocytosis. Keratohyalin granules are sparse to absent in VC and, while koilocytotic cells may be found in VC, they are decidedly less common than in VVL. In VVL, the rete pegs (if apparent at all on some biopsies) are elongated, thin, pointed, radially oriented, and sometimes branched, whereas in VC they are bulbous, rounded, or club-shaped and exhibit less branching. VVL is also usually positive on immunostaining for HPV, whereas verruca carcinoma is uniformly negative.

E. Treatment and Prognosis

Simple endoscopic excision is usually curative, although one patient did experience two local recurrences five and seven years, respectively, after initial excision (2).

IX. BENIGN NONEPITHELIAL TUMORS OF THE LARYNX

A. Introduction

The most comprehensive reviews of benign conditions of the larynx have been by New and Erich and Holinger and Johnston (1,2). A critical analysis of these studies as well as our own experience at the University of Pittsburgh (3) (Table 2) indicates that mesenchymal tumors comprise 8% to 17% of all benign laryngeal neoplasms. Hyperkeratosis, leukoplakia, cysts, myxomas (which probably represent vocal cord nodules), and various inflammatory lesions, which were included in the former two studies, but not in the above calculations, are not considered by us to be neoplasms. A review of some of the more common benign nonepithelial tumors of the larynx follows.

B. Hemangioma

Hemangiomas of the larynx can be divided into two groups: those occurring in infants and those occurring in adults.

Hemangiomas in Infants

Hemangiomas of the larynx in infants arise primarily in the subglottis and, as such, are ominous, potentially life-threatening lesions because of airway compromise. Fortunately, they are uncommon, as evidenced by only 17 cases being diagnosed over a 10-year interval at the Children's Hospital in Boston (4) and, in a review of 866 congenital lesions of the larynx, Holinger and Brown identified only 13 (1.5%) that were hemangiomas (5).

They are more common in females by a 2:1 ratio and almost invariably present during the first six months of life. The infant is typically asymptomatic at birth, but during the ensuing weeks to months (average age at diagnosis 3.6 months), develops

varying degrees of respiratory embarrassment, often confused with the "croup" (6,7). Cough, cyanosis, and dysphagia may also be apparent, but hemoptysis is distinctly uncommon. The symptoms are episodic and vary from hour to hour or from day to day, depending on the degree of vascular engorgement. Forty-five to fifty percent of patients also have additional hemangiomas in locations other than the subglottis. Most of these are cutaneous, rarely visceral (6,7).

At laryngoscopy, one sees a pink to blue, sessile, compressible submucosal mass of the subglottis, usually on the left side. In a review of 116 patients, Bitar et al. noticed the lesion to be bilateral in 22% of cases, left-sided and posterior in 21%, circumferential in 21%, left-sided and unilateral in 16%, right-sided and unilateral in 6%, posterior in 5%, right-sided and posterior in 2% and unknown in 7% (7). The degree of airway narrowing ranged from 10% to 99% (mean 65%). Some hemangiomas are even apparent on imaging examination. Others are inconspicuous and difficult to identify even at autopsy, because of postmortem emptying of blood vessels.

Although it is commonly stated that biopsies should be avoided because of the risk of excessive bleeding and aspiration, Shikhani et al. refer to 82 patients with subglottic hemangiomas who underwent biopsies and, of these, only 2 experienced significant bleeding (6). The diagnosis in most instances can be established without biopsy if one pays close attention to the age of onset, symptomatology, and laryngoscopic findings in conjunction with cutaneous hemangiomas.

The tumors are most often solitary and limited to the subglottis, but on occasion, may involve the true vocal cords or trachea, or both. Multifocal hemangiomas of the upper aerodigestive tract are rare, but have been described (8).

Pathologically, subglottic hemangiomas are usually of the capillary type (92%) (6) (Fig. 32). Cavernous (4%) and mixed capillary-cavernous types (4%) are uncommon. Some may even be cellular enough to

Table 2 Benign Neoplasms of the Larynx at the Eye and Ear Institute Pavilion of Pittsburgh and Presbyterian University Hospital (1955–1993)

Type	Number	% of total
Squamous papilloma	326	80.7
Oncocytic papillary cystadenoma	35	8.7
Granular cell tumor	12	3.0
Hemangioma	9	2.2
Neurofibroma	3	0.7
Lipoma	3	0.7
Chondroma	3	0.7
Lymphangioma	2	0.5
Paraganglioma	2	0.5
Neurilemoma	2	0.5
Fibrous histiocytoma	2	0.5
Rhabdomyoma	2	0.5
Pleomorphic adenoma	1	0.2
Nodular fasciitis	1	0.2
Fibromatosis	1	0.2
Total	404	100%

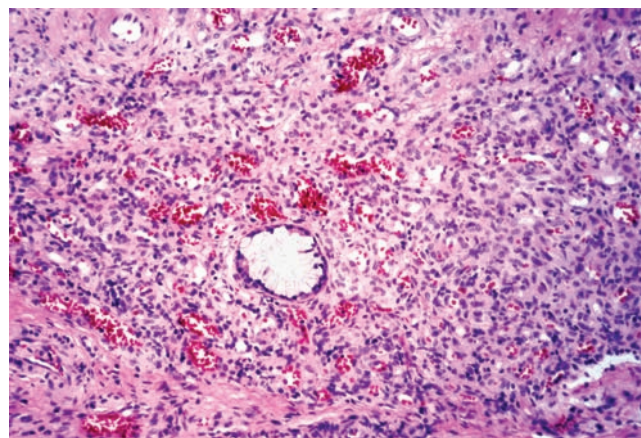


Figure 32. Subglottic capillary hemangioma with entrapped mucous gland (H&E, 200 $\times$).

qualify as benign hemangioendotheliomas. They are typically confined to the lamina propria, but may extend to involve the perichondrium of the underlying cartilage or invade between the tracheal rings to lie external to the trachea (9).

Because of the constant threat of asphyxiation, some form of therapy is usually necessary. Tracheotomy with a “watch and wait” approach for spontaneous involution, as is commonly used and seen in cutaneous hemangiomas, is associated with 4% to 46% mortality in subglottic hemangiomas (6,7). Other forms of therapy have been used with varying degrees of success and complications. Among these are included intralesional and systemic steroids, interferon, sclerosing agents, electrocautery, radioactive gold implants, cryosurgery, laser ablation, surgical excision, or a combination of these procedures (6,7,10). Variables that have an impact on the form of therapy and outcome depend on age (younger patients have more proliferative lesions), size of the lesion, location, and degree of airway compromise (7).

Hemangiomas in Adults

In contrast with laryngeal hemangiomas of infancy, which are primarily subglottic in origin and often life-threatening, hemangiomas in the adult larynx arise primarily in the supraglottis and rarely compromise the airway. They also differ from the infantile type in that they are more common in men (67% of all cases) and are usually of the cavernous type (11) (Fig. 33). Hoarseness, cough, dysphagia, and occasionally, hemoptysis are the predominant symptoms. Pregnancy, as in the case reported by Mugliston and Sangwan, may have an adverse effect on preexistent laryngeal hemangiomas, causing an increase in growth and exacerbations of symptoms (12).

Because adult hemangiomas tend to be of the cavernous type and composed of large blood vessels,

laser therapy is largely ineffective. Surgical excisions are usually required.

The vascular stage of a vocal cord nodule-polyp is often confused with a hemangioma of the true vocal cord. See “Differential Diagnosis” in the discussion of vocal cord nodules-polyps above.

C. Neurofibroma and Neurilemoma

Neurofibromas and neurilemmomas are uncommon tumors in the larynx, representing in our experience only 1.2% of all benign larynx neoplasms (Table 2). In 1993, only about 130 cases were reported in the literature (13–15).

They typically occur in the 30- to 60-year-old age group but have been found in patients from birth to old age (13–27). Although some studies indicate a slight male predominance (61%), others suggest that they are more common in females by a ratio of 3:2 (16,19).

Most arise submucosally in the supraglottic larynx in the vicinity of the aryepiglottic folds, false vocal cords, or arytenoids, presumable from branches of the superior laryngeal nerve (14) (Fig. 34). Symptoms are slow to evolve and consist of a fullness or sensation of a foreign body in the throat, cough, hoarseness, and occasionally respiratory distress.

The incidence of neurofibromas versus neurilemmomas of the larynx is unknown, for studies often lump the two lesions together under the generic term of “neurogenic tumors.” In our series of five cases, three were classified as neurofibromas and two as neurilemmomas (Table 2).

The distinction between these two neoplasms can be difficult or even impossible or small diagnosis. In this instance, a diagnosis of “benign nerve sheath tumor” would be appropriate.

Although neurilemmomas are usually single tumors, neurofibromas may be either solitary or occur in association with neurofibromatosis (16,20,22,24,26). Neurofibromatosis, however, rarely

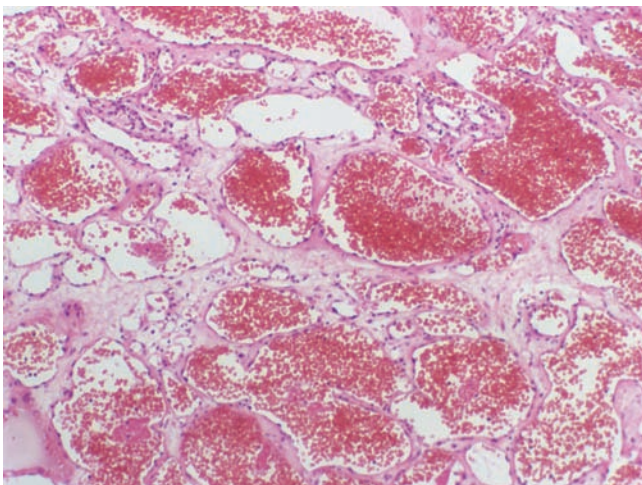


Figure 33. Supraglottic cavernous hemangioma in a 46-year-old man (H&E, 200×).

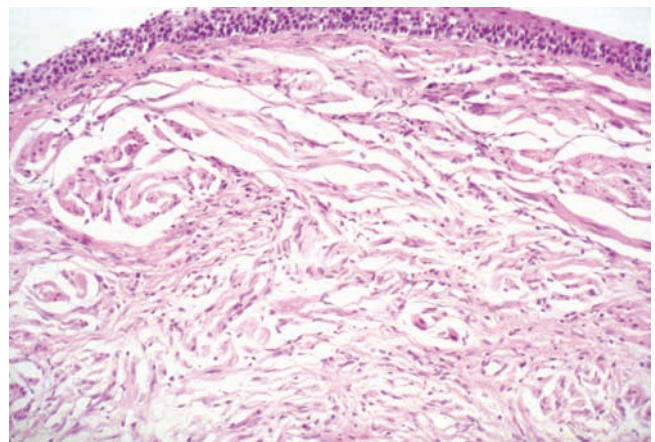


Figure 34. Neurofibroma of epiglottis (H&E, 200×).

involves the larynx. In a review of 257 cases of neurofibromatosis, White et al. identified only one patient with a neurofibroma of the larynx (18). Nonetheless, examples of laryngeal neurofibroma associated with neurofibromatosis have been clearly documented (20,22,26).

Conservative excision is the treatment of choice. For small tumors, this can be accomplished endoscopically, whereas larger ones may require an open surgical procedure. If incompletely excised, local recurrence may develop. The plexiform neurofibroma is more problematic. These lesions are often more extensive and "invasive" and to completely excise might require loss of some laryngeal function. In this instance, a subtotal excision might be appropriate in order to preserve the integrity of the larynx (27,28).

D. Lipoma

Approximately 112 lipomas of the larynx and hypopharynx have been described as of 2002 (29). At the University of Pittsburgh, it represents only 0.7% of all benign laryngeal neoplasms (Table 2).

It is more common in individuals in the seventh decade of life (range 8–83 years), and the majority are men (68%) (30–33). It typically presents in the supraglottic larynx in the area of the aryepiglottic fold, false vocal cord, or ventricle, areas that normally contain fat (Fig. 35). In some instances it may arise in adjacent anatomical sites and project into the larynx.

Most are solitary lesions, but on occasion, may coexist with lipomas in other body sites. At least one case has been described in association with benign symmetric lipomatosis (Madelung's disease) (34).

The tumors are sessile to polypoid and manifest with dyspnea, change in quality of voice, snoring, or a sensation of foreign body in the throat. Polypoid lesions may even result in acute airway obstruction through a ball-valve effect.

A CT scan can be extremely helpful, not only in localizing the lesion, but also in establishing the

diagnosis (35). Fat is the only soft tissue with a density lower than water.

Because laryngeal lipomas are often deep-seated, biopsies must also be deep or the lesion will be missed. Treatment depends on the size and location of the lesion. Small tumors can usually be removed effectively through an endoscope, whereas larger ones will require an external approach.

Although most lipomas of the larynx are of the "usual" type, unusual variants have been described. Among these are included myxoid lipoma (36), spindle cell lipoma (37), intramuscular lipoma (38), and hibernoma (39).

Lipomas may recur if incompletely excised (31). Such recurrences, however, must be meticulously evaluated because some liposarcomas of the larynx are often low-grade and initially mistaken for lipomas (40).

E. Leiomyoma

Leiomyomas are benign tumors of smooth muscle that primarily occur in the uterus, gastrointestinal tract, and skin. They are exceptionally rare in the larynx. In a review of 7684 leiomyomas at the University of Witwatersrand, in which the location was known, Farman observed only 1 that occurred in the larynx (41). None was found in a review of 404 benign laryngeal tumors on file at the University of Pittsburgh (Table 2).

Pathologically, leiomyomas can be divided into three types: conventional, vascular, and epithelioid. All of these have been described in the larynx.

Conventional Leiomyoma

These tumors in the larynx have been described in all age groups, but primarily in adults, and are somewhat more common in males (42–46). The supraglottis is the preferred site, especially in the region of the ventricle, false vocal cord, and aryepiglottic fold. Glottic and subglottic leiomyomas are uncommon.

Most are smaller than 3 cm and vary from sessile to polypoid. Obstructive airway symptoms and hoarseness are the usual presenting complaints. Excision, either through an endoscope or an open technique, is the treatment of choice. Subtotal removal will almost assuredly result in recurrence.

Vascular Leiomyoma (Angiomyoma)

Vascular leiomyomas of the larynx are more unusual than the conventional type, with fewer than 10 cases reported in the literature as of 1994 (47–49). They are more common in men, usually older than 50 years. About half have occurred in the supraglottic larynx, particularly in the region of the ventricle and aryepiglottic fold, and about half in the subglottis.

Dyspnea, hoarseness, and the sensation of a foreign body in the throat are the usual symptoms. A few patients may even present with acute airway obstruction.

Clinicians should be aware that biopsies or attempts to remove vascular leiomyomas endoscopically



Figure 35. Lipoma of false vocal cord (*gross*).

may be accompanied by profuse bleeding that is difficult to control. Consequently, some advocate that these tumors in the larynx should always be excised through an external approach for better hemostatic control.

Epithelioid Leiomyoma (Bizarre Leiomyoma, Leiomyoblastoma)

There have been at least two documented cases of epithelioid leiomyoma of the larynx (50,51). One occurred in a 53-year-old man, who presented with a one-year history of hoarseness and was found to have a 5-cm tumor of the left true vocal cord that was removed under general anesthesia using a suspension microlaryngoscope (50). He was reported free of the disease 28 months later.

The other case occurred in a 49-year-old woman who presented with a one-year history of hoarseness (51). A 1-cm mass was demonstrated submucosally in the left true vocal cord, which was removed by multiple microlaryngoscopic procedures. No additional follow-up was provided.

F. Other Tumors

Rhabdomyomas, granular cell tumors, chondromas, and other nonepithelial tumors are discussed elsewhere in this book.

X. KERATOSIS WITH AND WITHOUT DYSPLASIA

A. Introduction

The clinical significance of such terms as leukoplakia, hyperplasia, atypia, dysplasia, and keratosis as applied to isolated lesions of the larynx continues to be a confusing and controversial topic for both otolaryngologists and pathologists. This is largely due to the use of ambiguous and inconsistent terminology, the lack of unanimous agreement on the definition of these terms, failure of the clinician to obtain a representative biopsy, and the subjectivity of the pathologist interpreting the biopsy. It is also particularly frustrating when pathologists continue to invent new terms for the same lesion. For instance, it is now fashionable in some medical circles to speak of laryngeal intraepithelial neoplasia (LIN), laryngeal intraepithelial lesion (LIL), squamous intraepithelial neoplasia (SIN) and squamous intraepithelial lesion (SIL) and then grade the abnormality as I, II, or III. Such terms, as far as we are concerned, are only additional new synonyms for dysplasia. They do not enhance our understanding of the lesion and serve only to introduce additional confusing terms for the clinician to deal with. Furthermore, the terms "LIN" and "SIN" are misleading. They indicate a neoplasm when in reality many of these lesions are reversible.

Nevertheless, there are strong proponents of each of these classifications. Table 3 shows the three most popular schemes and the approximate equivalent terms of each. Preference depends on one's training, bias, and local custom. Our bias is in favor of the more traditional system of dysplasia—carcinoma in situ

Table 3 Classification of Premalignant Lesions of the Larynx

2005 WHO Classification	SIN	Ljubljana Classification SIL
Squamous cell hyperplasia		Squamous cell (simple) hyperplasia
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia ^a
Moderate dysplasia	SIN 2	Atypical hyperplasia ^b
Severe dysplasia	SIN 3 ^c	Atypical hyperplasia ^b
Carcinoma in situ	SIN 3 ^c	Carcinoma in situ

^aBasal/parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter the lower grade of precursor lesions.

^b"Risky epithelium." The analogy to moderate and severe dysplasia is approximate.

^cThe advocates of SIN combine severe dysplasia and carcinoma in situ. Abbreviations: SIN, Squamous intraepithelial neoplasia; SIL, squamous intraepithelial lesions.

Source: World Health Organization. Classification of Tumors. Pathology and Genetics. Head and Neck Tumors, Barnes L, Eveson JW, Reichart P, Sidransky D, eds., Lyon, IARC Press, 2005. Used with permission.

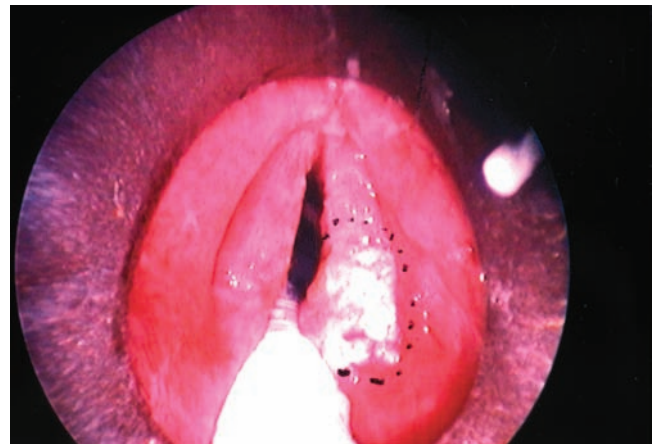


Figure 36. The vast majority of reactive and dysplastic lesions of the larynx present as white patches or leukoplakia (area outlined by black dots) Direct laryngoscopic exam of the larynx.

(CIS), preceded by the term "keratosis," e.g. keratosis with moderate dysplasia. The use of "keratosis" as part of the diagnosis is arbitrary, especially since it has no prognostic significance. However, considering that the vast majority of reactive—preneoplastic lesions of the larynx manifest as keratosis or white patches (leukoplakia), it does serve as a confirmatory marker indicating that the clinician has indeed biopsied and/or removed the intended lesion (Fig. 36).

Because of possible confusion, it is appropriate that a discussion of this subject begin with a series of definitions.

B. Normal Histology

At birth, the larynx is lined entirely by ciliated respiratory epithelium. As the individual ages, the respiratory epithelium is gradually replaced by non-keratinizing, stratified squamous epithelium to the point that, in the normal adult, the larynx is lined

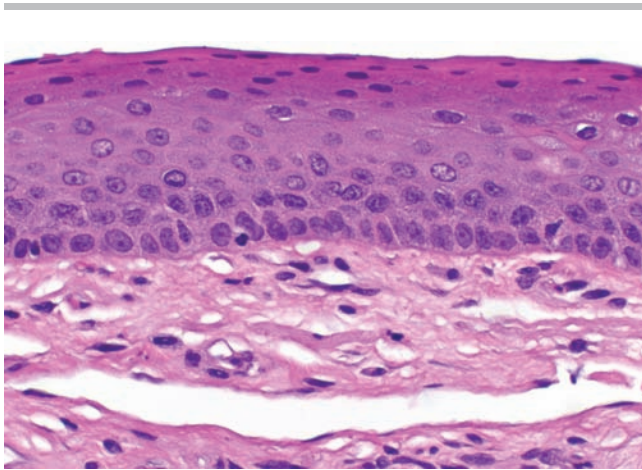


Figure 37. Right true vocal cord biopsy showing normal maturation. Note the basal cells with their long axes perpendicular to the basement membrane. As the cells approach the surface, they become round, acquire intercellular bridges and ultimately lie with their long axes parallel to the basement membrane. There is no surface keratinization (H&E, 100 $\times$).

entirely by squamous epithelium, with the exception of two areas—the ventricles and subglottis—which continue to be lined by respiratory epithelium. Infrequently, one may see small patches of persistent respiratory epithelium in an otherwise typical squamous mucosa of the adult supraglottic larynx.

The normal nonkeratinized squamous mucosa of the true vocal cords is about 5 to 10 cells thick. The cuboidal to columnar cells immediately adjacent to the basement membrane, so-called basal, reserve or germinal cells, have ovoid nuclei and lie with their long axes perpendicular to the membrane (Fig. 37). Mitoses, if seen at all, are normally limited to these or immediately adjacent cells. With increasing maturation, the nuclei become round and vesicular to hyperchromatic, the cytoplasm increases in volume, intercellular attachments (desmosomes) become apparent, and cells assume a polygonal shape. As the squamous cells approach the surface, they become flattened and lie parallel to the basement membrane. The epithelial cells that lie above the basal cells are, at times, referred to as prickly cells, the squamous cell layer, or the stratum spinosum.

Mucoserous glands are rather abundant in the larynx, particularly in the epiglottis, ventricles, false vocal cords, and subglottis. They are, however, sparse to absent in the true vocal cords, which has therapeutic implications when managing CIS.

C. Hyperplasia

The term “hyperplasia” refers to a thickening of the epithelium due to an absolute increase in number of cells. It may be limited to the basal cells (basal cell hyperplasia) or the prickly cells (acanthosis), or it may involve both groups of cells. If extensive, irregular tongues of basement membrane—enclosed epithelium may extend into the underlying stroma, so-called

pseudoepitheliomatous hyperplasia. In the case of the true vocal cords, anything more than 10 cells in thickness can be considered as abnormal or hyperplastic.

D. Keratosis

This denotes the presence of keratin (orthokeratin) on an epithelial surface and is often, but not always, associated with a prominent granular cell layer. Since the laryngeal mucosa is not normally keratinized, the term “hyperkeratosis” is redundant.

E. Parakeratosis

Retention of nuclei within the keratin layer is referred to as parakeratosis. It usually represents faulty maturation or a more rapid turnover of epithelial cells than seen in keratosis. Otherwise, in the larynx, it has no clinical significance.

F. Dyskeratosis

Dyskeratosis represents faulty or premature keratinization of individual squamous cells.

G. Atypia-Dysplasia

The use of these terms varies according to pathologist. Strictly speaking, atypia refer to cellular aberrations, such as pleomorphism, variation in nuclear size and shape, presence or absence of nuclei, increased nuclear—cytoplasmic ratios and thickness and irregularities of the nuclear and cell membranes. Dysplasia, in turn, is concerned with disturbances of growth and maturation, such as loss of polarity and crowding of cells, dyskeratosis, keratin pearl formation, and the presence of normal and abnormal mitoses in the superficial epithelial layers.

Some pathologists, however, equate atypia and dysplasia as being synonymous and apply the terms interchangeably. Others use “atypia” when the cellular changes are thought to be benign or reactive as occurs in various inflammatory, degenerative-regenerative, and traumatic conditions and “dysplasia” when the findings raise concern about a premalignant condition. In this chapter, we use the term dysplasia when we are concerned about premalignant changes.

Dysplasia is graded as *mild* (Grade I) if the abnormal changes are confined to the inner one-third of the epithelium, *moderate* (Grade II) if the aberration involve from one-third to two-thirds of the thickness of the epithelium, and *severe* (Grade III) if the changes extend from two-thirds to just short of full-thickness involvement.

H. Carcinoma In Situ

CIS is classically defined as full-thickness epithelial disarray and atypia without violation of the basement membrane. Severe dysplasia, SIN-III, and LIN-III are regarded by some as synonyms.

I. Leukoplakia

This is a clinical term, not a pathologic diagnosis, used to describe any white lesion on a mucous membrane that cannot be rubbed off with the hand. Histologically, such lesions range from being totally innocuous to invasive carcinoma.

J. Erythroplakia

This is another clinical term used to describe any red area on a mucous membrane. In contrast to leukoplakia, erythroplakia is a more ominous lesion often associated with high-grade dysplasia or in situ or superficially invasive carcinoma. It is uncommon in the larynx.

K. Keratosis with and without Dysplasia

The above-defined abnormalities may exist individually or in combination. There is, however, a tendency in some medical centers, which we endorse, to combine these, as well as other closely related terms, into two broad categories: keratosis without dysplasia (KWOD) and keratosis with dysplasia (KWD) (Table 4) (1–3). KWOD refers to either a normal, hyperplastic, or atrophic squamous epithelium covered by a scale of orthokeratin or parakeratin (Fig. 38). Whether the scale is orthokeratin or parakeratin has no clinical relevance; therefore, it does not warrant a separate category and can be safely included under the generic term “keratosis.” KWD is similar in all respects to KWOD except for the presence of abnormal epithelial cells and growth (Figs. 39–41).

Although most keratoses are flat, occasionally they are papillary. When papillary, the term “papillary keratosis” can be used, followed by whether or not there is dysplasia and, if so, how severe, e.g., papillary keratosis with moderate dysplasia (see discussion on “keratinized papillomas” above) (Figs. 26–29).

The frequency of each of the categories of keratoses with and without dysplasia is shown in Table 5.

L. Clinical Features

KWOD and KWD are clinically indistinguishable and typically present as a localized thick, white patch that may be flat or papillary. On rare occasions, it may be diffuse, obstruct the glottis, and even necessitate a tracheotomy (1).

Table 4 Synonyms for Keratosis with and without Dysplasia

Keratosis without dysplasia	Keratosis with dysplasia
Hyperplasia	Atypia
Acanthosis	Dysplasia
Squamous hyperplasia	Atypical hyperplasia
Keratosis	SIN or SIL, I, II, III
Parakeratosis	LIN or LIL, I, II, III

Abbreviations: SIN, squamous intraepithelial neoplasia; SIL, squamous intraepithelial lesion; LIN, laryngeal intraepithelial neoplasia; LIL, laryngeal intraepithelial lesion.

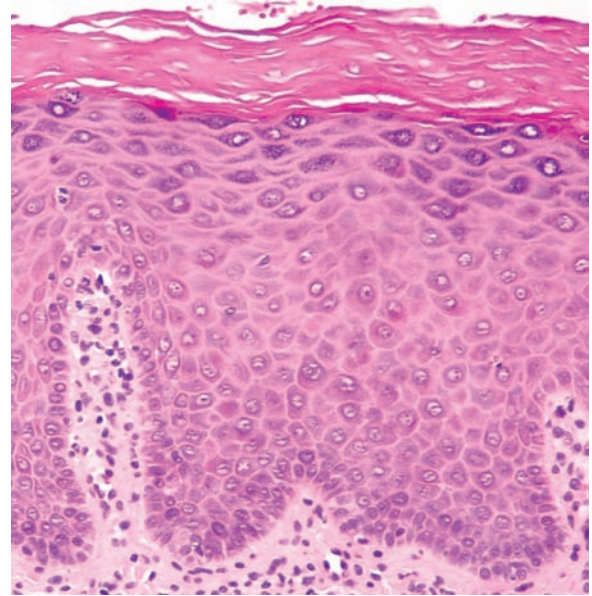


Figure 38. Keratosis without dysplasia. Note the surface layer of keratin and prominent keratohyaline granules. There is no atypia or dysplasia (H&E 200×).

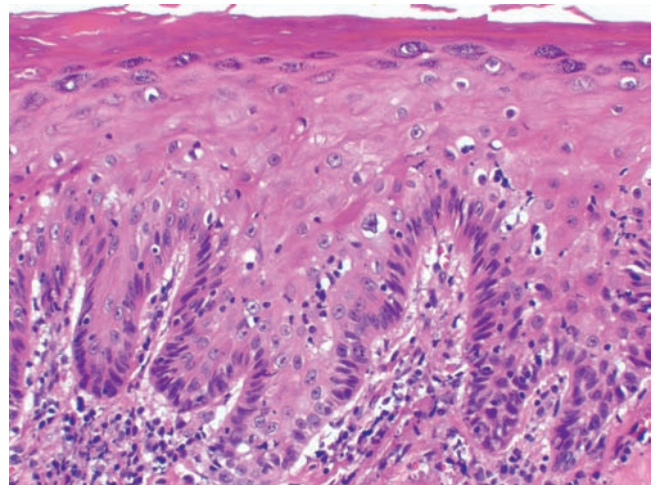


Figure 39. Keratosis with mild dysplasia (H&E, 200×).

KWOD and KWD average about 1 cm in greatest dimension and can occur anywhere in the larynx. Most, however, arise from the true vocal cords with no significant lateralization to either side. Bilateral involvement of the true vocal cords occurs in about 25% to 30% of cases (3,6,7). As might be expected, hoarseness or a change in quality of the voice are the most common symptoms. Most patients (75–85%) are male (3,8). The mean age at diagnosis, according to Sllamniku et al. is 52 years for patients with KWOD and 59, 58, and 62 years, respectively, for those with keratosis with mild, moderate and severe dysplasia (3).

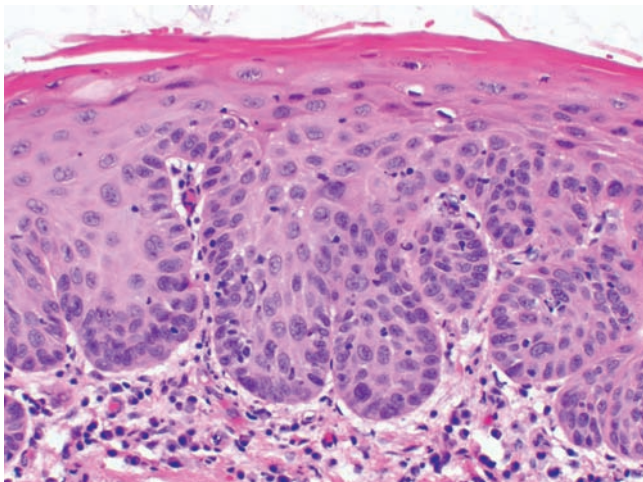


Figure 40. Keratosis with moderate dysplasia (H&E, 200×).

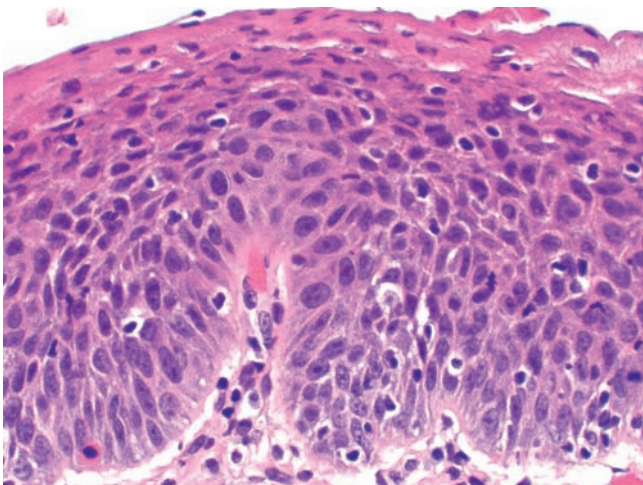


Figure 41. Keratosis with severe dysplasia (H&E, 200×).

Table 5 Frequency of KWOD and KWD

Category	Silamniko (3) (N = 921)	Gallo (4) (N = 259)	Ricci (5) (N = 207)
KWOD	66%	55%	46%
KWD, mild	22%	22%	22%
KWD, moderate	3%	11%	20%
KWD, severe	10%	12%	11%

Abbreviation: KWOD, keratosis without dysplasia; KWD, keratosis with dysplasia.

M. Treatment and Prognosis

Treatment consists of excisional biopsy, using either forceps or vocal cord stripping, with thorough microscopic evaluation to rule out malignancy. If the biopsy shows only KWOD or mild to moderate KWD, no further treatment is necessary except for periodic

follow-up. Whether patients whose biopsies show severe KWD need additional therapy depends on the extent of the lesion, local definition of “severe dysplasia” (some equate severe dysplasia and CIS as synonyms), and the experience of the clinician. If the etiology can be identified, it should be eliminated. Most often this means giving up smoking, which is the single most common cause. In most studies, only 5% to 20% of patients are nonsmokers (6,8–10). Other responsible factors include alcohol, chronic infections, voice abuse, vitamin A deficiency, and exposure to various industrial or atmospheric irritants.

Both KWOD and KWD are potentially reversible, the former more so than the latter; however, as the severity of dysplasia increases, so does the likelihood of persistence or progression of disease. Taken together, the incidence of recurrence or (persistence?) following initial therapy varies from 15% to 30% (8). In approximately 7% of cases, KWOD will progress to KWD (6,9).

In a collective review of 1502 cases of KWOD and 1188 cases of KWD, the risk of subsequent development of invasive squamous carcinoma is approximately 3% to 5% and 16% to 19%, respectively (Tables 6 and 7) (1–6,9,11–18). For keratosis with mild, moderate, and severe dysplasia, the risks are, respectively, 5.7%, 20%, and 23.8% (Table 8) (2–5,15,17). Of those patients with laryngeal keratosis who eventually develop invasive carcinoma, the average latency period from the time of diagnosis of keratosis to carcinoma is 3.8 years (3).

According to Blackwell et al., laryngeal biopsies of patients that progress to invasive carcinoma compared with those in whom the disease remains stable or regresses more often demonstrate (i) abnormal mitoses, (ii) prominent mitotic activity within the middle or upper third of the mucosa, (4) (iii) proliferation of small uncommitted cells above the lower one-third of the mucosa, (iv) moderate to severe nuclear pleomorphism, and (v) moderate to severe stromal inflammation (17).

Studies for DNA ploidy may also have prognostic significance. Although not absolute, there is increasing

Table 6 Incidence of Invasive Carcinoma Developing in Patients with Keratosis Without Dysplasia

Author (yr) (Ref.)	Total number of cases	Number of invasive carcinomas	% of all cases
McGavran (1960) (1)	66	1	1.5
Norris (1963) (9)	30	1	3.3
Gabriel (1973) (11)	50	3	6
Henry (1979) (6)	29	1	3.4
Crissman (1979) (12)	50	0	0
Hellquist (1982) (2)	98 ^a	2	2
Gillis (1983) (13)	7	2	28.6
Kalter (1987) (14)	38	2	5.3
Silamniko (1989) (3)	604	18	3
Hojislet (1989) (15)	128 ^a	6	4.7
Cuchi (1994) (16)	167	14	8.7
Blackwell (1995) (17)	6	0	0
Gallo (2001) (4)	143	6	4.1
Ricci (2003) (5)	86	2	2.3
Total	1502	58 (3.9%)	5.2 (average)

^aIncludes some patients with mild atypia.

Table 7 Incidence of Invasive Carcinoma Developing in Patients with Keratosis with Dysplasia

Author (yr) (Ref.)	Total number of cases	Number of invasive carcinomas	% of all cases
McGavran (1960) (1)	18	2	11.1
Norris (1963) (9)	86	5	5.8
Gabriel (1973) (11)	55	4	7.3
Henry (1979) (6)	14	3	21.4
Crissman (1979) (12)	42	3	7.1
Hellquist (1982) (2)	63 ^a	12	19
Gillis (1983) (13)	17	5	29.4
Kalter (1987) (14)	92	20	21.7
Silamniku (1989) (3)	317	44	13.9
Hojislet (1989) (15)	19	8	42.1
Cuchi (1994) (16)	74	23	31
Blackwell (1995) (17)	50	12	24
Gallo (2001) (4)	116	13	11.2
Ricci (2003) (5)	111	10	9
Jeannon (2004) (18)	114	28	24
Total	1188	192 (16.2%)	18.5 (average)

^aIncludes only grade II and III dysplasia.

Table 8 Incidence of Invasive Carcinoma in Patients with Keratosis with Mild, Moderate and Severe Dysplasia

Author (yr) (Ref.)	Mild (Carcinomas: total cases)	Moderate (Carcinomas: total cases)	Severe (Carcinomas: total cases)
Hellquist (1982) (2)	2:98 ^a	3:24	9:39 ^b
Silamniku (1989) (3)	15:204	4:23	25:90
Hojislet (1989) (15)	6:128 ^a	4:9	4:10
Blackwell (1995) (17)	3:26	5:15	4:9
Gallo (2001) (4)	4:56	6:28	3:32
Ricci (2003) (5)	2:42	5:36	3:21
Total	32:554 (5.7%)	27:135 (20%)	48:201 (23.8%)

^aIncludes some cases of keratosis without dysplasia.

^bIncludes some cases of carcinoma in situ.

evidence that laryngeal biopsies that demonstrate aneuploidy correlate with genomic instability that is likely to persist or eventuate in carcinoma (19–22).

XI. CARCINOMA IN SITU

A. Introduction

In the past, squamous cell CIS of the larynx, hereafter referred to as CIS, was found most often adjacent to and rarely remote from invasive squamous cell carcinoma. However, since 1968 with the introduction of microlaryngeal techniques developed by Kleinsasser, surgeons and pathologists have become increasingly aware that it can exist as an isolated lesion, without an invasive component (1). Currently, it represents 1% to 13% of all laryngeal carcinomas (2–10).

B. Clinical Features

Although CIS can occur anywhere within the larynx, most arise from the true vocal cords, especially the

anterior one-third. Sometimes, it may involve the entire cord, the anterior commissure, or both vocal cords. Multifocal areas are not uncommon. The rarity of CIS in the supraglottic and subglottic larynx is probably because these are clinically “silent” areas, which allows a prolonged asymptomatic interval for the lesion to become invasive.

CIS has the same propensity for men as invasive laryngeal carcinoma, with most studies indicating a male/female ratio between 3:1 and 8:1 (8,11,12). It occurs over a broad age range, with a mean/median age of 60 to 65 years (12–18). Hoarseness is the usual presenting symptom.

C. Pathology

CIS (also referred to as squamous intraepithelial neoplasia or lesion, type III) is defined histologically as a neoplastic process in which the normal epithelium is completely replaced by cells with malignant characteristics that do not extend beyond the basement membrane. As such, the cells demonstrate loss of polarity and maturation, normal and abnormal mitoses, occasional dyskeratosis, increased nuclear/cytoplasmic ratios, and anisonucleosis. Infrequently, the abnormal cells may extend down into ducts of submucous mucoserous glands, but such an involvement is still within the realm of CIS (Fig. 42).

CIS that consists of a rather uniform population of small basaloid cells, with no surface maturation or keratinization, as seen in classic CIS of the uterine cervix, is uncommon in the larynx (Fig. 43). More often, CIS of the larynx, and especially of the true vocal cords, presents as a white patch (leukoplakia) with a full-thickness disarray and admixture of basaloid and dyskeratotic squamous cells, covered by a scale of orthokeratin or parakeratin (Fig. 44).

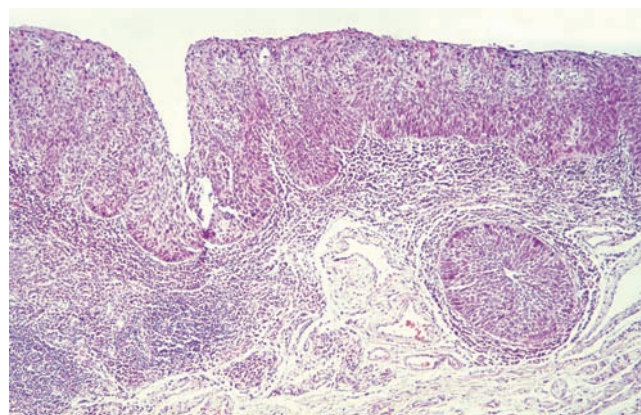


Figure 42. Carcinoma in situ with involvement of duct of mucoserous gland. The basement membrane around the duct is intact. This should not be mistaken for invasive carcinoma. In the overlying surface component, note that the cells in the lower half are more basaloid (“uncommitted”), whereas those in the upper half appear more “squamous” (H&E, 100×).

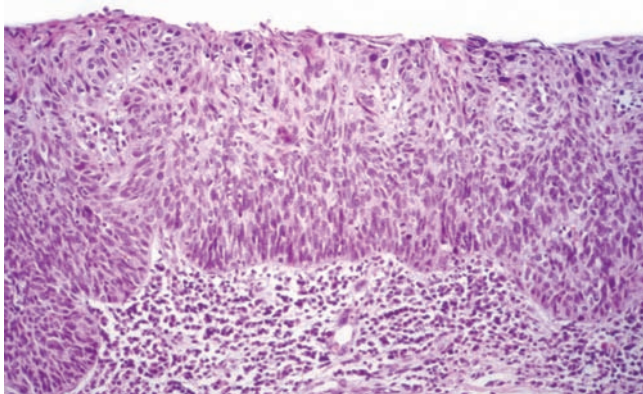


Figure 43. Higher magnification of the surface mucosa shown in Figure 42. With the absence of keratin on the surface, this carcinoma-in situ would present clinically as a red patch or erythroplakia (H&E, 200 $\times$).

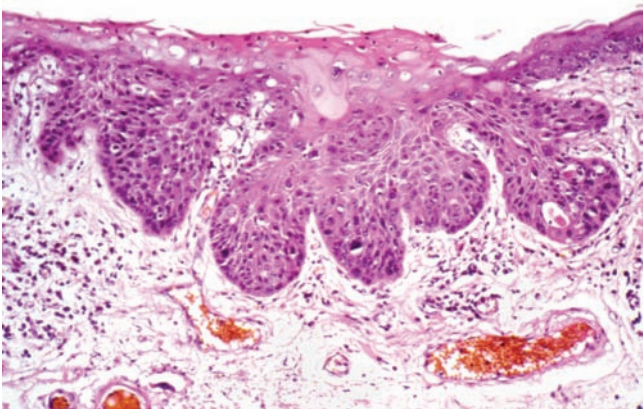


Figure 44. More typical carcinoma in situ of the true vocal cord composed of abnormal cells with more "squamous" features, covered by a scale of parakeratin. Atypical nuclei are also apparent in the parakeratin (H&E, 200 $\times$).

D. Molecular-Genetic Data

Studies indicate that those dysplastic laryngeal lesions that show loss of heterozygosity at 3p21, 5q21, 9p21 and 17p13 are more likely to progress to carcinoma (19).

Much interest has also been expended toward developing reliable immunomarkers that could be used to identify lesions destined for malignant progression. Although data indicate that alteration in p53 plays a role in the early stage of malignant transformation of some (most) squamous cell carcinomas of the larynx, there is ongoing debate on whether its continued immunoexpression, either alone or in combination with other biomarkers (p16, p21, Bcl-2), has any predictive value (20–26).

E. Treatment and Prognosis

Effective treatment of laryngeal CIS consists of understanding the natural history of the disease. Unfortunately, this is largely unknown for several reasons. First, although the pathology is relatively straightforward, there is an inordinate amount of subjectivity involved in the interpretation of biopsies. The inconsistencies in diagnosis of CIS among various pathologists and even the same pathologist studying the same case at different times is well known and accounts for wide differences in the reported incidence of CIS either progressing or regressing. Second, the natural history of CIS is probably altered by the procedure used to establish the diagnosis; that is, the biopsy, which may contain the entire lesion. Third, a variety of therapeutic modalities, ranging from watch-and-wait to irradiation and surgery have been employed in the management of these patients. Fourth, the biopsy may not be representative. Fifth, CIS at times may be multifocal and not unrecognized. Sixth, follow-up has often been inconsistent, inadequate, or nonexistent. And, seventh, in contrast with uterine cervical cytology, which is a reliable means of detecting and following patients with abnormal conditions of the cervix, laryngeal cytology is inconvenient and cumbersome and, consequently, has not been widely accepted.

With the foregoing limitations in mind, it is understandable why the incidence of CIS progressing to invasive carcinoma reported in the literature has varied from 1.5% to 90% (Table 9). When viewed collectively, these studies indicate the incidence to be in the range of 20% to 25% with an average latent period from diagnosis of CIS to invasion of 3 to 5 years (2,7,8,10–12,14,27–38).

Treatment of CIS of the vocal cords is not standardized. Options include vocal cord stripping, laser surgery, cordectomy, hemilaryngectomy, radiation, and/or a combination of these procedures. The choice of initial therapy should be tailored to the patient and depends on the extent of tumor, age, and reliability of the patient for follow-up, and the experience of the physician. Small lesions can usually be treated conservatively with stripping. The advantages of stripping are that it can be accomplished in one session, as opposed to six to seven weeks for radiation, and all the specimens can be sent to pathology for thorough examination to rule out carcinoma, whereas this opportunity is lost with radiation. When stripping fails, the salvage rate with radiation is good (16).

The paucity and/or absence of mucoserous (salivary) glands in the true vocal cords allows one to use the mucosal stripping procedure with relative impunity. However, there is an extensive tubuloalveolar system of glands in the region of the anterior commissure (40–42). These glands at times may be located at some distance from the mucosal opening of their ducts and, therefore, if involved by CIS, may not be removed by simple mucosal stripping. Consequently, when CIS involves the anterior commissure (an adverse sign associated with poor local control), additional therapy, such as laser ablation or even irradiation, may be warranted.

Table 9 Incidence of Carcinoma In Situ of Larynx Progressing to Invasive Carcinoma

Author (yr) (Ref.)	Total cases of CIS	Number of invasive carcinomas ^c	% of invasive carcinomas
Altmann (1952) (2)	29	1	3.4
Kleinsasser (1968) (27)	20	18	90
Miller (1971) (28)	203	32	15.7
Holinger (1974) (29)	8	2	25
Som (1976) (30)	24	4	16.7
Pene (1976) (31)	26	1	3.8
Elman (1976) (7)	81 ^a	13	16
Hintz (1981) (11)	45	22	48.9
Hellquist (1982) (32)	39 ^a	9	23.1
Gillis (1983) (33)	8	3	37.5
Maran (1984) (8)	28	2	7.1
Kalter (1987) (34)	8	4	50
Shvero (1988) (35)	21	1	4.8
Crissman (1988) (36)	25	12	48
Rothfield (1991) (10)	13	2	15.4
Stenersen (1991) (37)	41 ^{a,b}	19	46.3
Small (1993) (38)	21	1	4.8
Murty (1993) (14)	37	8	21.6
Brooks (1993) (13)	12	2	16.7
Myssiorek (1994) (12)	41	16	39
Blackwell (1995) (39)	9	1	11.1
Le (2000) (16)	82	15	18.3
Spayne (2001) (17)	67	1	1.5
Garcia-Serra (2001) (18)	30	3	10
Total	918	192 (20.9%)	23.9% (average)

^aIncludes some patients with severe dysplasia.^bIncludes only patients who were treated with repeat biopsies. (Their group C).^cIncludes microinvasive and "ordinary" invasive carcinomas.

Abbreviation: CIS, carcinoma in situ.

According to Rothfield et al., the ultimate success of therapy may depend more on compulsive follow-up than the specific form of treatment (10).

XII. MICROINVASIVE (SUPERFICIAL) CARCINOMA OF THE LARYNX

A. Introduction

The use of the term *microinvasive carcinoma* (MIC), also known as superficially invasive carcinoma, as applied to lesions of the larynx, is very subjective, with no unanimous definition among pathologists. Fisher describes it as "a very small number of cells, perhaps a dozen or even just 50 that are in the entire lesion, and only just below the basement membrane" (1). Friedmann defines it as "scattered tongues or some discrete foci of invasion through the basement membrane" (2). Padovan uses the term for lesions limited to 2 mm of invasion (3). Crissman et al. use it for any "squamous carcinoma violating the preexisting epithelial basement membrane and limited to 1 to 2 mm of invasion from the site of origin without vascular invasion" (4). Our definition, which admittedly is arbitrary and lies between these extremes, is that of an invasive squamous cell carcinoma that extends into the stroma no more than 0.5 mm, as measure from the

epithelial basement membrane, with no evidence of lymphatic or vascular invasion (Figs. 45–47).

At times, either because of tangential embedding or inflammatory cells obscuring the epithelial-stromal interface, one cannot determine, with confidence, whether or not the lesion has violated the basement membrane (Fig. 48). In these instances, a diagnosis of "squamous cell carcinoma in situ, with questionable microinvasion" is appropriate.

Not all carcinomas evolve through a dysplasia-CIS sequence. Some are invasive without a significant

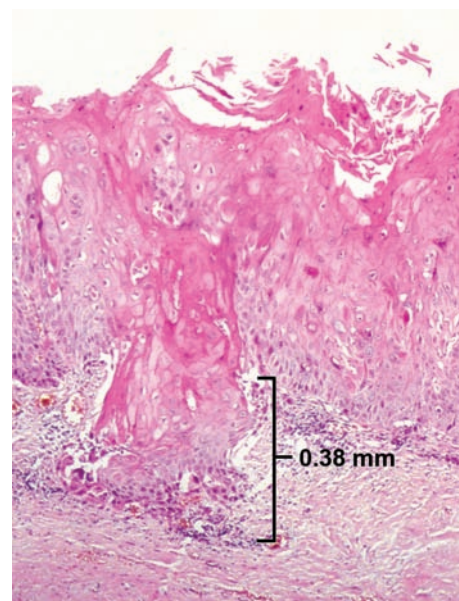


Figure 45. Microinvasive squamous cell carcinoma of the true vocal cord. The tumor extends 0.38 mm into the lamina propria, as measured from the adjacent intact basement membrane (H&E, 100×).

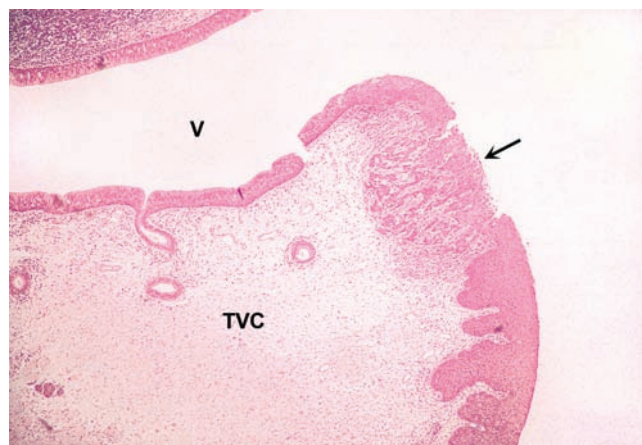


Figure 46. Incidental squamous cell carcinoma of the true vocal cord (TVC, arrow) found at autopsy. Note the ventricle (V) above. This carcinoma measured 0.8 mm and exceeded our definition of a microinvasive carcinoma (0.5 mm or less) (H&E, 20×).

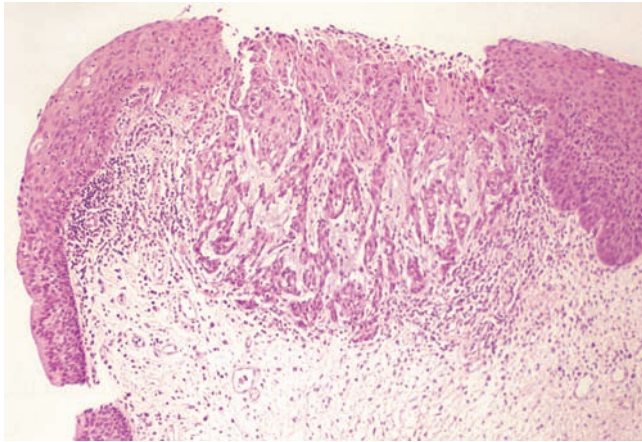


Figure 47. Higher magnification of the lesion shown in Figure 46.

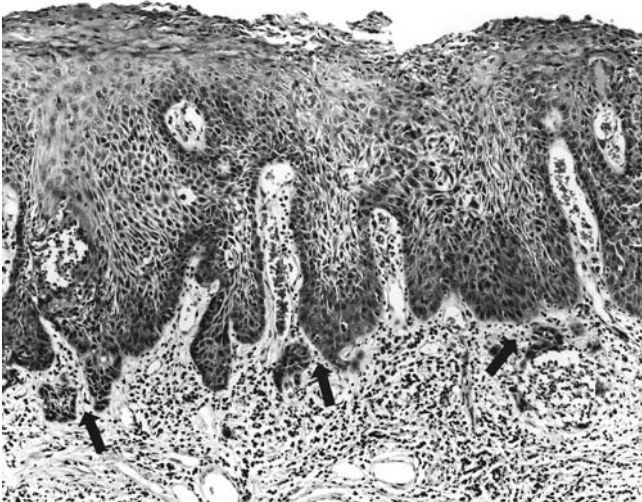


Figure 48. Is this microinvasive carcinoma or a tangential embedding issue (arrows)? If the dilemma cannot be resolved by deeper sectioning, then a diagnosis of “carcinoma in situ with questionable microinvasion” is appropriate (H&E, 100 $\times$).

mucosal component and appear to arise from the basal layer of epithelium. These are sometimes referred to as “drop-off” carcinomas (Fig. 49).

B. Clinical Features

MIC typically involves the true vocal cords, especially the anterior and middle thirds and presents as hoarseness (5). It is more common in men by a ratio of 3:1 and occurs over a broad age range, with a median of 65 years (6). In a review of 15 cases, Nguyen et al. observed the right true vocal cord to be involved in nine (60%), the left in four (27%) and both cords in two (13%) (6).

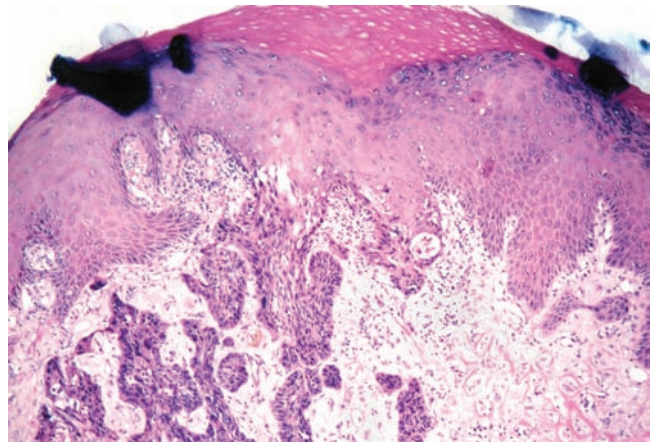


Figure 49. An invasive squamous cell carcinoma of the larynx that appears to arise from the basal layer of the mucosa. Note the absence of dysplasia or carcinoma in situ. These are sometimes referred to as “drop-off” carcinomas (H&E, 100 $\times$).

C. Treatment and Prognosis

Although the treatment of MIC is not standardized, there is a movement toward more conservative procedures, such as stripping the vocal cord mucosa with or without laser ablation (5–8). Stutsman and McGavran were among the first to recommend an ultraconservative approach; namely, endoscopic removal of the lesion, with periodic follow-up (9). This was based on their study of 60 patients with T1 glottic carcinomas who underwent hemilaryngectomy; in 20% (13 of 60 patients) of these no residual tumor was found, the lesion having been totally excised with the original biopsy. Therefore, if surgery or radiation were administered to all patients with biopsy-proven MIC, one in five would be receiving unnecessary therapy. The paucity or absence of mucoserous (minor salivary) glands in the true vocal cords, relative lack of lymphatics in the laryngeal glottis, and that recurrent lesions manifest early with hoarseness, are all conducive to such a nonaggressive approach.

However, the success of this form of therapy depends on compulsive follow-up, especially because these patients are at risk not only for local recurrence, but also for the development of new lesions. If the patient is not dependable for routine follow-up or is medically unable to undergo anesthesia for periodic laryngoscopic examination, then other alternatives, such as radiotherapy, should be considered (8). With a compliant patient and meticulous surveillance, the long-term prognosis is excellent.

XIII. SUPERFICIAL EXTENDING CARCINOMA

Superficial extending carcinoma (SEC) of the larynx and hypopharynx is the morphological counterpart of the “early” or “superficial” carcinoma of the esophagus and stomach (1–7). As such, it is defined in the larynx and hypopharynx as an early invasive

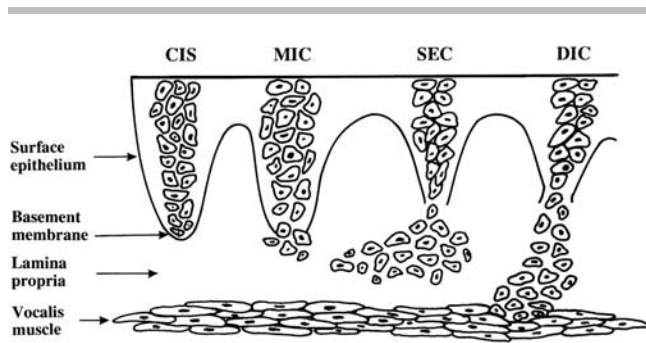


Figure 50. Diagram showing conceptual differences between carcinoma in situ (CIS), microinvasive carcinoma (MIC), superficial extending carcinoma (SEC), and deeply invasive carcinoma (DIC).

squamous cell carcinoma that does not extend beyond the lamina propria, regardless of the presence or absence of cervical lymph node metastasis (8,9). Whether SEC associated with positive cervical lymph nodes should still qualify as an early carcinoma is, however, open to debate.

The SECs vary considerably in size. Some are small, whereas others are quite large, with a prominent surface (mucosal) component and extensive involvement of the lamina propria, yet, by definition, they do not invade the adjacent muscle or cartilages. A component of CIS and chronic inflammation are additional frequently observed findings. A few may even be multifocal.

Conceptually, SEC is more than an MIC, but less than a deeply invasive carcinoma (one that invades muscle or cartilage) (Fig. 50). It differs from MIC in that MIC is predominantly a CIS with only focal superficial invasion of the lamina propria, whereas in SEC the lamina propria is often extensively involved.

Although SEC may be treated by a variety of conservative modalities, if recognized as such, the diagnosis, however, can be established with confidence only after the lesion has been totally excised and thoroughly examined histologically (10–15). The prognostic significance of this entity is unknown and must await the accrual of more patients with long-term follow-up.

XIV. SQUAMOUS CELL CARCINOMA OF THE LARYNX

A. Introduction

According to the American Cancer Society, cancer of the larynx accounts for 0.7% of all cancers and 1.1% of all malignant tumors in men and 0.3% in women (1). During 2006 there were 9510 new cases diagnosed in the United States, of which 7700 (81%) occurred in men and 1810 (19%) in women (1). For this same time period, there were 3740 deaths from the disease.

Squamous cell carcinoma accounts for 95% of these neoplasms. Most patients are in the fifth, sixth,

or seventh decades of life at the time of diagnosis, with an average of about 60 years. Less than 1% of laryngeal cancers occur in patients younger than 30 years of age.

Smoking and alcohol abuse are by far the principal risk factors and, of these, smoking is the more important. In fact, only 3% to 4% of all laryngeal carcinomas occur in nonsmokers (2,3). Other risk factors that have been proved, suggested, or debated include prior radiation exposure, HPV infection, genetic factors, air pollution, dietary deficiencies (vitamins A and C, and iron), chronic gastrointestinal reflux, and occupational exposure to wood dust, asbestos, nickel, mustard gas, hair dyes, gasoline fumes, paint, sulfuric acid, and rubber products (4–10).

Marked geographic variations exist in the frequency of laryngeal carcinoma, not only between countries, but also in different parts of the same country. Regions in India, Spain, Brazil, Italy, and France have the highest incidence, whereas areas in Japan, Sweden, and Norway have among the lowest (11). In general, urban environments tend to have higher cancer rates than rural (12).

In addition to variations in incidence, there are also geographic differences in the topographic distribution of tumors within the larynx. In parts of the former Yugoslavia, France, Italy, Spain, The Netherlands, and Finland, supraglottic tumors predominate, whereas in the United States, Canada, England, and Sweden, glottic lesions are more common (13) (Fig. 51). In Japan, the distribution of tumors between these two sites is about equal.

A noticeable increase in laryngeal carcinoma in women has also been observed over the last two decades, presumably owing to their increase in smoking (3,14). This is unfortunate because carcinoma of the larynx is a preventable disease. If only individuals would alter their lifestyles (stop smoking and drinking), over 90% of laryngeal carcinomas could be eliminated.

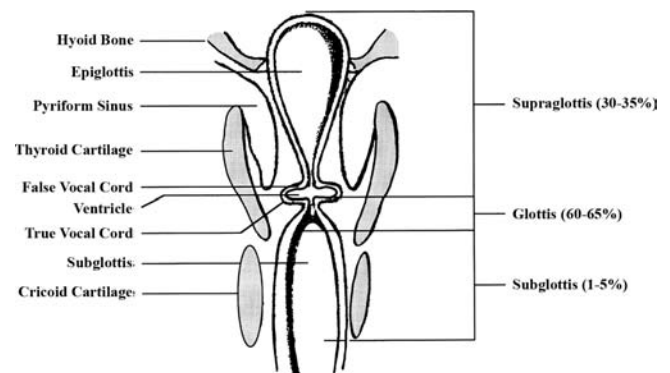


Figure 51. Diagram showing the subdivisions of the larynx and the relative frequency of squamous cell carcinoma involving each of these sites in the United States.

Anatomy and Embryology

The larynx anatomically extends from the tip of the epiglottis to the lower border of the cricoid cartilage (Fig. 51). The posterior boundary includes the posterior commissure mucosa, the mucous membrane covering the cricoid cartilage, the arytenoid region, and the interarytenoid space. The anterior limit is composed of the lingual surface of the epiglottis, thyrohyoid membrane, anterior commissure, thyroid cartilage, cricothyroid membrane, and the anterior arch of the cricoid cartilage.

The blood supply is by the superior laryngeal branch of the superior thyroid artery and the inferior branch of the inferior thyroid artery. The nerve supply is derived from two branches of the vagus nerve, the superior and inferior laryngeal.

The larynx can be subdivided into three regions: supraglottic, glottic, and subglottic (Fig. 51). The boundaries of each of these are described in the following sections. The term "transglottic" does not correspond to a specific anatomical site, but rather, is used to describe any tumor that crosses the ventricle.

The supraglottic larynx is derived embryologically from the third and fourth branchial arches (buccopharyngeal anlage); therefore, it is closely related to the oral cavity and oropharynx and, accordingly, more susceptible to ingested carcinogens (alcohol). The glottis and subglottis, on the other hand, arise from the sixth branchial arch (pulmonary anlage); therefore, they are more intimately related to the lungs and more susceptible to inhaled carcinogens (smoking) (15).

The growth and spread of laryngeal carcinoma is determined by the site of origin of the tumor and the anatomical barriers produced by the different laryngeal structures and compartments (16–19). Pathologists should be aware of at least three of these anatomical components, which are often not covered in standard textbooks of pathology: the anterior commissure tendon (Broyles' ligament), the pre-epiglottic space, and the paraglottic space. These structures represent the "weak points" of the larynx, whereby tumors may escape from the larynx into the soft tissue of the neck.

The anterior commissure tendon is especially important in glottic carcinomas that approach or involve the anterior commissure. It consists of a band of fibrous tissue 10 mm in length and 1 mm in width and contains both blood vessels and lymphatics (20). It serves to anchor the true vocal cords to the upper inner midline of the thyroid cartilage. It is important because at its attachment to the thyroid cartilage there is no perichondrium, thereby eliminating an important tumor barrier (21). This allows a more direct opportunity for tumor to invade the thyroid cartilage, the anterior soft tissue of the neck, or to involve the immediate subjacent subglottis.

The pre-epiglottic space is not a space, but rather, a roughly triangular area anterior to the epiglottic cartilage that is filled with adipose and loose areolar tissue (Fig. 52). It is bounded anteriorly by the hyoid bone, thyroid cartilage, and thyrohyoid membrane; posteriorly by the epiglottic cartilage and thyroepiglottic ligament; and superiorly by the hyoepiglottic ligament, which forms its base (22–28).

The paraglottic space is also not a space, but an area deep to the true and false vocal cords that contains adipose and loose areolar tissue (Fig. 53). It is bounded by the cricovocal membrane (conus elasticus) inferiorly, the thyroid cartilage laterally, the quadrangular membrane medially, and the pyriform sinus posteriorly (24,29). Superiorly, the paraglottic space is in continuity with the pre-epiglottic space. Although both spaces contain lymphatics and blood vessels, neither contains lymph nodes.

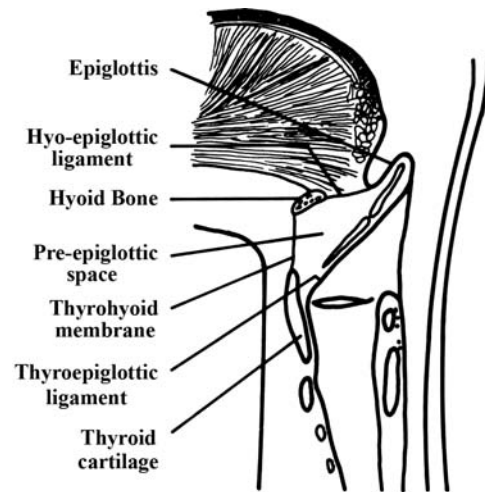


Figure 52. Diagram showing the pre-epiglottic space and its boundaries.

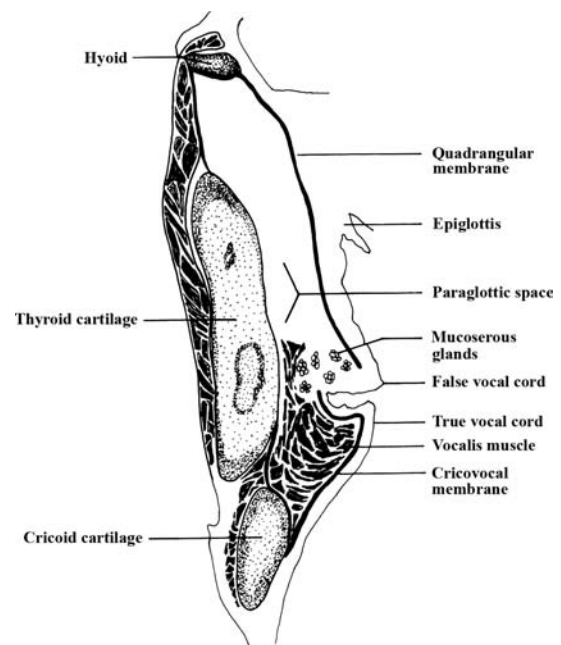


Figure 53. Diagram showing the paraglottic space and surrounding landmarks.

The pre-epiglottic and paraglottic spaces are important in understanding the growth and behavior of supraglottic and transglottic carcinomas, respectively. Once tumors bridge these spaces, they can spread with little resistance in the loose areolar tissue and eventually escape from the endolarynx into the soft tissue of the neck.

Staging

The TNM staging (*T*, tumor; *N*, nodes; *M*, metastasis) of carcinoma of the larynx is shown in Table 10 (30).

B. Supraglottic Carcinoma

The tip of the epiglottis and the aryepiglottic folds form the superior margin of the supraglottis. The inferior border is an imaginary horizontal plane passing through the apex of the ventricle (Fig. 51). The supraglottic larynx is composed of the epiglottis (both its lingual and laryngeal surfaces), aryepiglottic folds, arytenoids, false vocal cords, and ventricles (30). The epiglottis is divided into suprahoid and infrahyoid components by a plane at the level of the hyoid bone.

Supraglottic carcinomas account for 30% to 35% of all laryngeal carcinomas in the United States. Most patients with these tumors complain of dysphagia, change in quality of voice, sensation of a foreign body within the throat, or a neck mass. With more extensive disease, odynophagia, hemoptysis, and dyspnea may be noted.

The tumors tend to be large and moderately to poorly differentiated squamous cell carcinomas with pushing margins (Figs. 54 and 55). Most arise from the base of the epiglottis or from the false vocal cords. The epiglottis is involved alone in 45% to 55% of all cases or in combination with other sites in 70% to 90% of cases. The next most frequent site of origin is the false vocal cords (12–33%) followed by the aryepiglottic folds (8–21%). The remaining cases are equally divided between the ventricles (4–7%) and arytenoids (5–6%) (31–33).

From the base of the epiglottis—false vocal cord region, the tumors tend to spread upward toward the free margins of the epiglottis and aryepiglottic folds, or into the pyriform sinus or vallecula—base of tongue. On rare occasions, they may extend posteriorly to the arytenoids. Because of fenestrations in the epiglottic cartilage, invasion of the pre-epiglottic space occurs in 50% to 85% of cases (26,34–37), and when this occurs, there is a high incidence of lymph node metastasis (27,34,38,39) (Fig. 56). Although supraglottic carcinomas usually do not invade the glottis or thyroid cartilage, there are exceptions (40–43). Weinstein et al. indicate that when supraglottic carcinomas are associated with impaired vocal cord mobility and involve the paraglottic space, there is a high probability that the tumors have invaded the glottis or cartilaginous framework of the larynx (43). If so, then the patient is a candidate for a total rather than supraglottic laryngectomy.

The most important factor in determining prognosis is the presence of regional lymph node

metastasis, which averages 30% to 40% (range 23–60%) (33,36,37,42,44–53). If the tumor crosses the midline of the larynx, some have observed the incidence of contralateral or bilateral nodal involvement, either at or during the course of the disease, to range from 7% to 50% (49,55–59). Lutz et al., in a study of 202 supraglottic carcinomas, found the incidence of contralateral nodal metastases to be 18% and noted the risk of contralateral cervical metastases in patients with midline (epiglottic) lesions to be similar to that observed in patients who had lateral (aryepiglottic fold) lesions (37). The upper and midjugular lymph nodes are most often involved.

At the time of diagnosis, most supraglottic tumors are relatively large and, as such, are often treated by surgery and radiation. Because the neck, especially the contralateral neck, is the most common site of relapse, laryngectomy (either supraglottic or total) and bilateral selective neck dissections is emerging as the most preferred treatment (37,42,48,60–62).

Additional forms of therapy have also been used. For selected small volume tumors, an endoscopic-laser approach has been successfully used. In more advanced tumors (stage III and IV) there is evidence indicating that a treatment strategy involving induction chemotherapy and definitive radiation therapy may be effective in preserving the larynx in a high percentage of patients without comprising overall survival (64).

The overall five-year survival for all stages is about 65% to 75% (33,37,42,47,49,52–54,58,65). Only 5% to 15% of patients with supraglottic carcinoma develop clinical evidence of metastases below the clavicles (37,49,50,52,54,66,67).

Tumors that arise from the suprahoid epiglottis and aryepiglottic folds are often referred to as marginal or epilaryngeal lesions. As a group, they constitute 18% of all supraglottic carcinomas and behave more like hypopharyngeal carcinomas in that they often spread to the base of the tongue and are less prone to invade the pre-epiglottic space (13,68). There is controversy, however, about the prognosis of this group of lesions. Some authors indicate that marginal (suprahoid) tumors have a greater propensity for cervical lymph node metastasis and a poorer prognosis than infrahyoid tumors (13,69–72), whereas others have found the converse; that is, infrahyoid epiglottic tumors have a worse prognosis and a greater tendency for cervical lymph node metastasis than marginal (suprahoid) tumors (68).

C. Glottic Carcinoma

The American Joint Commission on Cancer defines the superior border of the glottis as a horizontal plane passing through the apex of the ventricle and the inferior border as a horizontal plane 1 cm below the apex of the ventricle (30) (Fig. 51). The components of the glottis include the true vocal cords and the anterior and posterior commissures. The true vocal cords average 14 to 16 mm in length in the adult male and 10 to 12 mm in the adult female (73). At their midpoint,

Table 10 Staging of Carcinoma of the Larynx

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
Supraglottis			
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility		
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx		
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)		
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)		
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures		
Glottis			
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility		
T1a	Tumor limited to one vocal cord		
T1b	Tumor involves both vocal cords		
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility		
T3	Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)		
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)		
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures		
Subglottis			
T1	Tumor limited to the subglottis		
T2	Tumor extends to vocal cord(s) with normal or impaired mobility		
T3	Tumor limited to larynx with vocal cord fixation		
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)		
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, ≥3 cm in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension		
N3	Metastasis in a lymph node, >6 cm in greatest dimension		
Distant Metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
Stage IVA	T3	N1	M0
	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
Stage IVB	T4a	N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

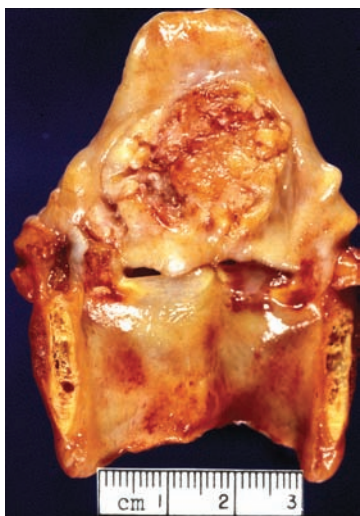


Figure 54. Gross appearance of a supraglottic carcinoma. The tumor is confined to the epiglottis.

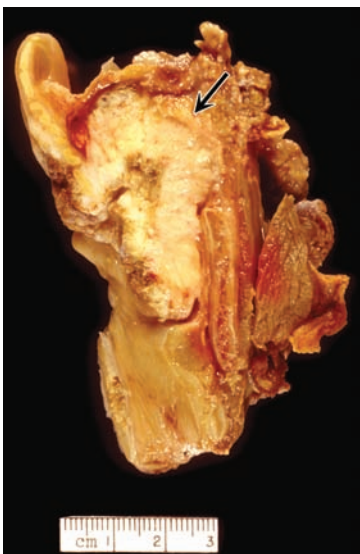


Figure 55. Vertical section through a supraglottic tumor. The tumor has a pushing margin and involves the pre-epiglottic space (arrow).

the vocal cords are approximately 5 mm in height, whereas anteriorly they are only 1 to 3 mm (74).

Glottic carcinomas account for 60% to 65% of all laryngeal carcinomas in the United States. Most arise from the anterior half of the cord and, as a consequence, produce hoarseness as a common early symptom (Figs. 57–59). They are equally distributed between the right and left true cords. Although only 1% to 9% of all cancers originate at the anterior commissure, depending on the series, it is involved secondarily in 10% to 46% of all glottic carcinomas

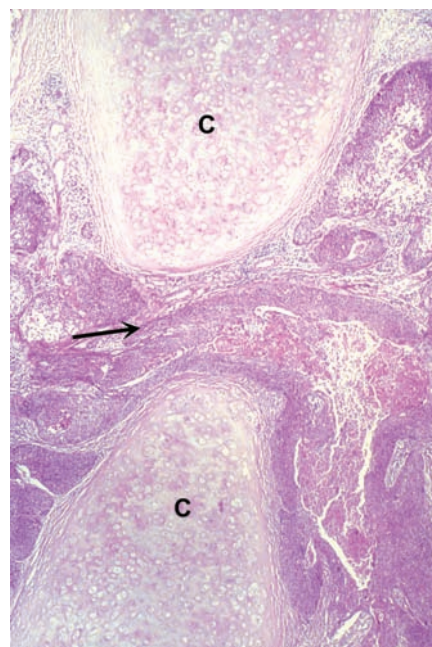


Figure 56. Squamous cell carcinoma of the epiglottis invading through fenestrations (arrow) of the epiglottic cartilage (c). Such defects allow easy access of tumor into the pre-epiglottic space (see Fig. 52).



Figure 57. Typical gross appearance of a glottic carcinoma arising primarily from the left true vocal cord (arrow), but also crossing the anterior commissure to involve the anterior portion of the right true vocal cord. The lesion was discovered incidentally at autopsy in a 60-year-old man who died of other causes.

(75–78). Carcinomas originating at the posterior commissure are exceptionally rare.

The tumor initially presents as an irregular area of mucosal thickening or ulceration and, eventually, as an exophytic or endophytic mass. Most are well to moderately differentiated squamous cell carcinomas, with either pushing or infiltrating borders.

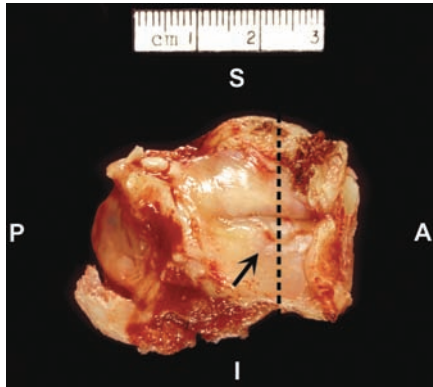


Figure 58. Hemilaryngectomy specimen. This is a voice-conserving procedure done for small carcinomas of the true vocal cord (arrow). It is important to orient the specimen for anterior (A), posterior (P), superior (S), and inferior (I) aspects. Sections should always be taken vertically through the true and false vocal cords and ventricle (line with hashmarks; see also Fig. 59).

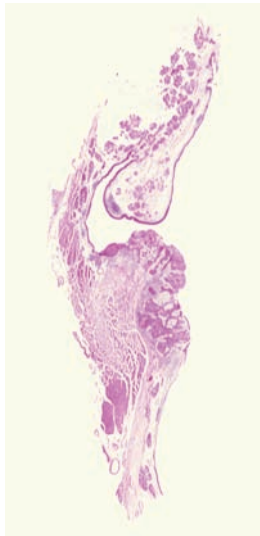


Figure 59. Histological section should always be taken vertically through the laryngeal glottis to preserve anatomical relations (see Fig. 58). Note the tumor arising from the true vocal cord encroaching on the underlying vocalis muscle (H&E, whole mount).

Because of the limited lymphatic supply and scant number of mucoserous glands in the true vocal cords, glottic carcinomas tend to remain localized for an extended time; therefore, they are amenable to cure if detected early (79,80). As the disease progresses, the tumor may extend along several pathways: (i) across the anterior commissure to the opposite true vocal cord; (ii) anteriorly through the anterior commissure

tendon (Broyles' ligament) to extend over or through the thyroid cartilage in the midline, with subsequent growth into the soft tissue of the neck; (iii) posteriorly to involve the arytenoids; (iv) subglottically, with the potential to pierce the cricothyroid membrane and grow into the soft tissue of the neck, or to gain access to the lymphatic channels that drain to the paratracheal and mediastinal lymph nodes; and (v) supraglottically, to involve the ventricle, false vocal cord, and epiglottis.

Before the carcinoma extends beyond the vocal cords, it often replaces or "fixes" the vocalis muscle, an ominous clinical sign (81). If the cord is not fixed and the carcinoma is superficial to the conus elasticus, the incidence of lymph node metastasis is less than 2%. A fixed vocal cord is associated with cervical node metastasis in about 25% of cases. Twenty to twenty-five percent of glottic carcinomas will demonstrate either supraglottic or subglottic extension (75,76,82). They do not invade the thyroid cartilage until there is more than 1 cm of subglottic extension (83).

The overall incidence of lymph node metastasis during the course of the disease varies from 0% to 6% for T1 lesions, 4% to 11% for T2 lesions, 14% to 22% for T3 lesions, and 25% to 41% for T4 lesions (84–86). The overall five-year survival rate for all glottic carcinomas is about 80% to 85% (75). The five-year survival rates range from 82 to 96% for T1 lesions, 51% to 85% for T2 lesions, 48% to 59% for T3 lesions, and 0% to 30% for T4 lesions (13). Risk factors associated with an increased incidence of locoregional failures include (i) prior tracheotomy, (ii) poor histological differentiation, (iii) subglottic extension of tumor of more than 1 cm, and (iv) histologically positive cervical lymph nodes (84,87,88).

Only about 3% to 6% of patients with glottic carcinomas develop clinical evidence of metastases below the clavicles (67,83,84). Those individuals with positive cervical lymph nodes that show extracapsular (extranodal) invasion into the surrounding perinodal soft tissue are more likely to develop distant metastases (84).

D. Subglottic Carcinoma

The American Joint Commission on Cancer defines the superior border of the subglottis as an imaginary horizontal plane 1 cm below the apex of the ventricle (30). The lower border is the inferior rim of the cricoid cartilage (Fig. 51). Tumors in this site account for 1% to 5% of all squamous carcinomas of the larynx seen in the United States (Fig. 60). They tend to be moderately to poorly differentiated, with infiltrating borders. Dyspnea and stridor are the most common symptoms. Almost one-third of the patients with these symptoms will require emergency tracheotomy to maintain an airway (89). The tumor usually spreads circumferentially and anteriorly through the cricothyroid membrane to involve the thyroid gland and paratracheal and prelaryngeal lymph nodes. It can also spread posteriorly below the thyroid cartilage and involve the cervical esophagus, medially into the cricoarytenoid



Figure 60. Rare example of primary subglottic carcinoma of the larynx (arrows). Note the attached right lobe of the thyroid gland.

joint to reach the hypopharynx, or inferiorly to involve the trachea.

About 15% to 25% (range 4–40%) of patients have cervical lymph node metastases, usually to the lower jugular chain (89–96). Lymphatic drainage of the subglottis consists of three main tributaries: one anterior and two posterolateral (97). The anterior group pierces the cricothyroid membrane to terminate in the prelaryngeal (Delphian) lymph node, which, in turn, drains to the pretracheal and supraclavicular nodes (91). The two posterolateral groups pierce the cricotracheal membrane and terminate in the paratracheal nodes, which are continuous with those in the superior mediastinum. Although only 15% to 25% (range 4–40%) of patients have positive cervical lymph nodes, about 50% have positive, but clinically undetectable, paratracheal lymph nodes (91). For this reason, Harrison advocates total laryngectomy with clearance of the paratracheal and superior mediastinal lymph nodes (91). Furthermore, one or both lobes of the thyroid should also be removed, for they may be involved in 10% to 20% of cases (98).

About half of patients with subglottic carcinoma die of local or stomal recurrences (91) and 15% to 20% will develop distant metastases, most often to the lungs and bones (89,98,99). The five-year survival rate most frequently quoted for subglottic carcinoma is about 40% (range 36–70%) (89–91,94,95).

Occasionally, glottic carcinomas with subglottic extension will exhibit a clinical course indistinguishable from a *de novo* subglottic carcinoma. In general, the greater degree of subglottic extension, the worse the prognosis and the more the tumor behaves as a subglottic primary.

E. Transglottic Carcinoma

The term “transglottic carcinoma” was coined by McGavran et al. in 1961 to designate those tumors that cross the ventricles to involve the supraglottis and glottis (and often the subglottis) (55) (Fig. 61). Unlike the latter terms, transglottic does not correspond to a specific anatomical site within the larynx.

Mendonca and Bryce are of the opinion that most transglottic carcinomas represent supraglottic extension of primary glottic carcinomas (82). In their experience, 25% of all glottic carcinomas extend across the ventricles. It is generally accepted that primary carcinomas of the ventricle are rare.

Not all transglottic carcinomas are large. Of 152 cases reviewed by Mittal et al., 31% were classified as T2, 39% T3, and 30% T4 (100). Twenty-six percent of their patients had cervical lymph node metastasis at presentation and another 19% subsequently developed positive lymph nodes during the course of their disease.

Most of these tumors are moderately differentiated squamous cell carcinomas, with infiltrating margins. The tumors characteristically spread within the paraglottic space and escape from the endolarynx by growing through the cricothyroid or thyrohyoid membranes, or by spreading submucosally into the pyriform sinus (Fig. 62).

In the series of Mittal et al., 70% of the tumors were confined to the larynx, and 30% demonstrated extralaryngeal growth (100). If the tumor is larger than 3.0 cm, there is a 75% chance that it has invaded the cricoid or thyroid cartilages, or both, especially the lower one-third of the latter (101). Extralaryngeal spread, invasion of the laryngeal cartilages, or both should be suspected in any patient whose transglottic carcinoma is accompanied by referred otalgia (102). The five-year survival rate is approximately 50% (100).

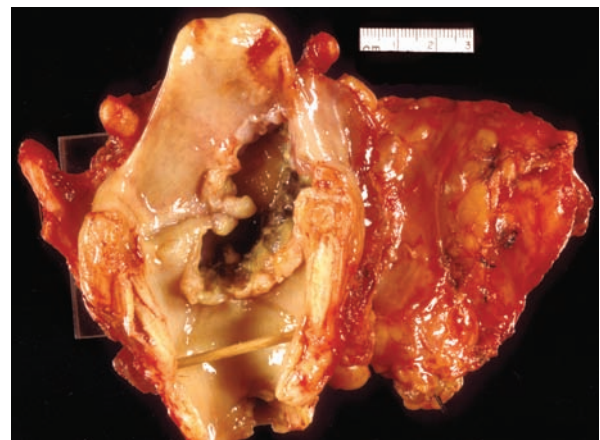


Figure 61. Total laryngectomy and right radical neck dissection. Note the large, ulcerated, transglottic carcinoma.

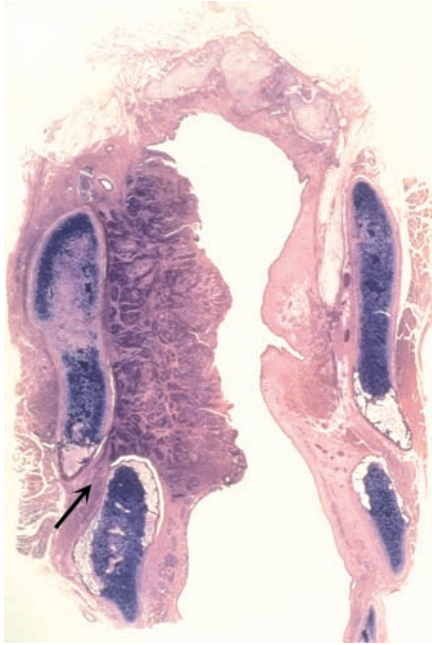


Figure 62. Coronal section of a transglottic squamous cell carcinoma of the larynx. Compare with the uninvolved (*normal*) right side. Note that the tumor fills the paraglottic space and is beginning to escape from the endolarynx by growing through the cricothyroid interspace (*arrow*).

F. Laryngeal Carcinoma in Children and Young Adults

Squamous cell carcinoma of the larynx is distinctly uncommon in individuals younger than 20 years of age (103–112). Zalzal et al. identified only one case in a 9-year-old girl among 1000 pediatric cancer patients treated over a 25-year time interval, for an incidence of only 0.1% (109). In 1984, 54 cases were recorded in the literature in individuals 15 years old or younger and, by 1987, only 21 cases had been documented in patients 10 years old or younger (105,107,109).

Most of these tumors have occurred in the region of the true vocal cords and have manifested clinically as hoarseness. In contrast with adults, however, the incidence of laryngeal cancer in children is significantly greater in girls (40% of all cases; 105).

For a long time, previous irradiation exposure, usually for recurrent respiratory papillomatosis, was the only known risk factor for patients in this age group. This is no longer true. The role of HPV and passive smoking are gaining more attention, and individuals who actively smoke and abuse alcohol are becoming increasingly younger (111,112).

Although some have indicated that cancer of the larynx is more aggressive in children than in adults, this remains to be proved (109). Delays in diagnosis and undertreatment of these young patients may partly account for this alleged difference in behavior.

Selected Prognostic Factors

Margins of Resection In the larynx, a margin of resection of only 2 mm is considered adequate. This is based on the work of Futrell et al., who found that patients whose tumors were 5 mm or more from the laryngeal resection margin had a 52% five-year survival, whereas those with positive margins had a 28% five-year survival (113). Individuals whose tumors were technically free, but within a 2 mm of the margin, had a five-year survival of 30%. They concluded that, in the larynx, margins of 2 mm or greater behaved similarly to widely clear margins, whereas those within 2 mm constituted positive margins. Bauer et al., in a study of hemilaryngectomy specimens, observed that 18% of patients with positive margins had local recurrences, as opposed to 6% of patients who had free margins, but yet developed local recurrences (114).

Cervical Lymph Nodes The status of the cervical lymph nodes is one of the most important factors that determine prognosis in laryngeal carcinoma. It is commonly stated that the presence of even one histologically positive lymph node decreases the five-year survival almost by half (113). Some investigators have observed that when cervical metastases are confined to lymph nodes, the survival rate is almost identical to that of those patients with histologically negative nodes (115–118). Only when the tumor extends beyond the lymph node into adjacent perinodal soft tissue—so-called extracapsular spread (ECS)—is prognosis significantly affected. According to these investigators, ECS is an ominous finding associated with a 50% or more reduction in patient survival, compared with individuals with positive lymph nodes without ECS, and when found, warrants additional therapy (radiation or chemotherapy) (115–118).

Invasion of Laryngeal Cartilages Invasion of the cartilaginous framework of the larynx, according to some, is an adverse prognostic indicator associated with an increased incidence of cervical node metastases and death from disease (38,102,119). It occurs primarily in transglottic, infrequently in glottic, and rarely in supraglottic carcinomas. In a study of 185 laryngectomy specimens removed for cancer and studied by serial histological sections, Kirchner observed that 50% of transglottic (28 of 65 cases), 20% of glottic (13 of 64 cases), and 0% of supraglottic tumors (0 of 65 cases) invaded the laryngeal cartilages (120).

When tumor invades cartilages, it typically does so in the area that has undergone ossification. As such, the lower one-third of the thyroid cartilage and the upper portion of the cricoid cartilage are the most vulnerable sites (120).

Stomal Recurrence Stomal recurrence, defined as a diffuse infiltration of tumor at the junction of the amputated trachea and skin, occurs in 1.7% to 14.7% (average 6%) of all patients who have undergone laryngectomies (121–123). It is one of the most feared complications of this procedure, because it is relatively resistant to further therapy and, once diagnosed, the average survival is only 9 months (101). Seventy percent of patients who experience stomal recurrence

do so within the first year after laryngectomy and 98% within 2 years (121).

The precise pathogenesis of stomal recurrence is unknown. Factors that have been suggested include (a) unrecognized tumor at the margin of initial resection, (b) development of a second primary malignant neoplasm, (c) tumor implantation at the time of tracheotomy or at the time of primary surgery, and (d) recurrence secondary to metastases in the paratracheal or pretracheal lymph nodes.

It is generally agreed, however, that individuals with tumors that involve the subglottis, either primarily or secondarily, are especially at risk for developing this complication. Whether preoperative or emergency tracheotomy enhances the risk is highly controversial.

Invasion of the Thyroid Gland Invasion of the thyroid gland occurs in 3% to 14% of all laryngeal carcinomas and is characteristically associated with advanced tumors (124,125). Of 23 cases of laryngeal carcinoma in which the thyroid was involved, Gilbert et al. noted that (a) all 23 cases tumors had invaded one or more of the laryngeal cartilages, (b) 16 of 23 (70%) tumors demonstrated perineural or vascular invasion, and (c) 21 of 23 tumors (91%) extended 10 mm or more subglottically (124).

Involvement of the thyroid may be by direct extension of tumor from the larynx (65%) or by metastatic spread to one or both lobes of the thyroid (35%). Either mechanism is associated with a poor prognosis, for 78% patients with involvement of the thyroid will die of their disease within 3 years of diagnosis and often within 1 year (117).

The work of Gilbert et al. further underscores the need to remove one or both lobes of the thyroid gland when dealing with all primary subglottic carcinoma or any laryngeal tumor that has 10 mm or more of subglottic extension (124).

Multiple Primary Malignancies Patients with laryngeal carcinomas will develop a second primary malignant tumor in 10% to 24% of cases (85,126–128). Seventy percent of these additional primaries will occur in the respiratory and upper aerodigestive tracts and most will appear within 2 years of treatment of the index tumor (126,128).

The lung is, by far, the most common site of occurrence of the second primary, which is unfortunate because pulmonary carcinomas are generally more life-threatening than laryngeal tumors. The association of laryngeal with pulmonary carcinoma is strongest for those tumors that arise in the supraglottic larynx. Patients with supraglottic tumors have a 14 times greater chance of developing lung cancer than the normal population and are 3 times more likely to develop a second primary tumor in the lung than those with glottic primaries (127,129–131).

Whether patients who present with lung cancer are at increased risk for subsequent laryngeal carcinoma is unknown (132). Most patients with lung cancer, however, do not live long enough to assess this possibility.

Tumor (DNA) Ploidy Flow cytometric studies on squamous cell carcinoma of the larynx indicate that

17% to 90% of all tumors are aneuploid (133–138). The clinical significance of ploidy patterns in the larynx, however, is both confusing and controversial. Some investigators indicate that there is no correlation between tumor ploidy and survival, whereas others indicate that patients with aneuploid tumors have a more favorable outcome (129,130). Still others, conversely, have found that diploid tumors are associated with a better prognosis (139). Although Rua et al. have noted that the overall survival rates of patients with diploid and aneuploid tumors are comparable, they did observe that aneuploid tumors with a well-differentiated pattern are associated with a poor prognosis (136).

Laryngeal ploidy patterns have also been used to predict response to irradiation and chemotherapy. Again, the results are confusing. Some investigators have observed that nondiploid tumors respond better to both irradiation and chemotherapy, whereas others have found no relation between tumor ploidy and subsequent response to either of these therapeutic modalities (135,139–142). Walter et al., on the other hand, indicate that T1N0M0 glottic tumors that are aneuploid are more radioresistant than are diploid lesions and should be treated primarily with surgery (137).

Part of the foregoing controversy may be related to tumor (DNA) heterogeneity. El-Naggar et al. studied 21 squamous cell carcinomas of the larynx by flow cytometry and observed that 76% were heterogeneous in DNA content (138). According to these investigators, the calculated probability of missing aneuploidy if only one, two, three, or four tissue samples were analyzed was 33%, 17%, 8%, and 3%, respectively.

G. Molecular Genetic Data

There is much interest in identifying biomarkers that could be used to stratify patients with laryngeal carcinomas into those who could be managed conservatively (radiation therapy) versus those who are in need of more aggressive therapy (surgery). The two most widely studied markers have been p53 and Ki-67 (143–146).

It is generally agreed that p53 when used alone, has no predictive value for local recurrence, survival or response to radiation (143–145). Studies reporting the role of Ki-67 index in predicting response to radiation have produced, on the other hand, conflicting results (144,145,147–149). Part of this Ki-67 controversy may be related to whether the radiation is administered by routine or accelerated fractionated schedules. Rapidly growing tumors not only exhibit a greater initial response to radiation but also a greater likelihood of tumor repopulation with the use of a routine six-week course of radiotherapy as compared with slowly growing tumors. By keeping the total dose of radiation the same but giving it over a five rather than a six-week interval (accelerated fractionated therapy), slowly growing tumors are less likely to repopulate the tumor site and tend to have a better prognosis.

XV. SPINDLE CELL CARCINOMA, SARCOMATOID CARCINOMA, CARCINOSARCOMA

A. Introduction

This malignant biphasic tumor has been referred to by a variety of names, including spindle cell carcinoma (SPCC), pseudosarcoma, pleomorphic carcinoma, metaplastic carcinoma, sarcomatoid carcinoma, and collision tumor. Pathologically, it is composed of a squamous cell carcinoma, either in situ or invasive (rarely an adenocarcinoma or neuroendocrine carcinoma) and a spindle cell component that may vary from bland to pleomorphic. The former component is often small and elusive, requiring numerous sections for demonstration, whereas the latter tends to form the bulk of the tumor. As the plethora of names might indicate, its histogenesis, especially the spindle portion, is disputed. Is it a squamous cell carcinoma, with a benign reactive stroma, or is the entire lesion just a peculiar squamous cell carcinoma in which the squamous cells have assumed a spindled (pseudosarcomatous) appearance (1,2)? Or does it represent a collision tumor (squamous cell carcinoma growing next to a sarcoma), or a carcinosarcoma (a mixed epithelial-mesenchymal neoplasm arising from a single stem cell in which both elements are intermingled) (3,4)?

Contrary to initial belief, it is now apparent that the spindle component is capable, in some instances, or metastasizing either independently or in conjunction with the squamous cell carcinoma (5–7). This would seem to dispel the notion that the spindle portion is always reactive. By light microscopy, one often finds zones in which malignant squamous cells appear to transform into spindle cells. Tissue cultures have also confirmed that squamous cells can grow in a spindled pattern (8). On the other hand, enzyme histochemistry on fresh-frozen tissue suggests that the spindle cells are more compatible with fibroblasts or histiocytes than with epithelial cells (9).

Immunohistochemical studies have shown variable results. In some instance, the spindle cells have exhibited only epithelial (cytokeratin, epithelial membrane antigen) or mesenchymal markers (vimentin, actin, desmin, myoglobin), whereas others have expressed both epithelial and mesenchymal differentiation (10–18). Ultrastructurally, some investigators have found evidence supporting a mesenchymal origin of the spindle cells (6,9,19), whereas others contend that they are epithelially derived (2,20). To further confuse the issue, a few tumors, usually those occurring in areas of previous irradiation may contain metaplastic bone or even malignant osteoid and cartilage (4,12). A few may even exhibit skeletal muscle differentiation (17,20). The source of these heterologous elements—whether epithelial, mesenchymal, or even myoepithelial—is the subject of ongoing controversy and heated debates, for it strikes at the very heart of our traditional histogenetic classification of tumors.

Molecular data now indicate, rather definitively, that these tumors have a monoclonal origin from a noncommitted stem cell, which gives rise to both components (22–39).

There are those who seemingly use the term “spindle cell carcinoma,” rather loosely and are willing to apply to it any carcinoma associated with a spindle cell component, even in the presence of heterologous elements. With this generic approach, one could rightfully argue that synovial sarcoma is also an example of a spindle cell carcinoma. After all, it is biphasic, and the spindle cells characteristically stain for cytokeratin.

The term *spindle cell carcinoma* does not address the sarcomatous component present in some, but not all, of these tumors. One simply cannot choose to overlook the sarcomatous elements, because they may also metastasize, albeit rarely, and may, therefore, warrant additional therapy. The use of the popular term *metaplastic carcinoma* is also equally disconcerting because it too does not convey to the clinician the potential dual composition of this group of neoplasms.

The literature on SPCC has mostly focused on the concept of carcinomas undergoing “metaplasia” into various types of sarcomas. Is the converse also true? Can sarcomas undergo metaplasia into carcinomas? For instance, a significant number of alleged leiomyosarcomas can express cytokeratin on immunostaining (30). Are these examples of metaplastic sarcomas and, therefore, the mesenchymal counterpart of metaplastic carcinomas?

As a corollary to the foregoing discussion, there is a growing school of thought that tumors should be classified according to their degree of differentiation, rather than their presumed histogenesis or cell of origin (31,32). If one carries the cell of origin concept to its logical conclusion, there would be only two categories of tumors in the entire field of pathology: a benign zygoma and a malignant zygoma.

Data have accumulated indicating that neoplasms are not static, but are evolutionary in composition, responding to inherent genetic changes, the microenvironment, or therapeutic manipulation. Presumably, each tumor carries a partial or complete genetic composition of its host and, as such, may exhibit a uniform or variable phenotypic expression during its life span. We agree entirely with Gould that “it may prove useful to classify certain groups of neoplasms on the basis of what they in fact are, as defined by a series of appropriate phenotypic-differentiation marker expressions, rather than on the basis of questionable assumptions about their origin” (31). In other words, if a malignant biphasic spindle cell tumor stains only for epithelial markers, it should be designated as a spindle cell squamous carcinoma. If a similar tumor expresses both epithelial and mesenchymal markers or contains heterologous mesenchymal elements, it should be called a carcinosarcoma.

It should be emphasized that the term “carcinosarcoma” used in this context indicates tumor differentiation and not presumed histogenesis; that is, it does not imply that the tumor arises from two separate clones of cells, one being epithelial and the other mesenchymal. It is generally accepted that most, if not all, tumors originate from a single clone. If a clone should develop along divergent lines into epithelial and mesenchymal elements, the term carcinosarcoma

Table 11 Classification of Spindle Cell Carcinomas

1. Squamous cell carcinoma with reactive stroma	Spindle cells are bland and negative for epithelial markers; cells may stain for histiocytic markers
2. Spindle cell squamous carcinoma	Spindle cells stain positive for epithelial markers (keratin, EMA) or EM shows epithelial features
3. Carcinosarcoma	Epithelial and spindle cells intermingled; spindle cells are negative for epithelial markers but may stain for desmin, myoglobin, etc.; or presence of malignant osteoid or cartilage
4. Collision tumor	Carcinoma growing adjacent to a sarcoma without significant intermingling; sarcoma should be negative for epithelial markers and EM shows no epithelial features

Abbreviation: EM, electron microscopy.

would seem to be appropriate, calling attention, both clinically and pathologically, to both components of the tumor.

We believe that SPCC, as is currently used, is a generic term that encompasses four different categories of tumors that are potentially separable only by the use of immunohistochemistry or electron microscopy. These include squamous cell carcinoma with a reactive or desmoplastic stroma, spindle cell squamous carcinoma (note addition of the word *squamous*), carcinosarcoma, and collision tumor. (Table 11).

It has been suggested, however, that spindle cell squamous carcinoma and carcinosarcoma may represent a spectrum of a single entity and that the two share a similar prognosis (11,33–35). The finding of individual tumor cells that coexpress both epithelial and mesenchymal immunomarkers does add credence to this hypothesis (12). However, to suggest that they have a similar prognosis is undoubtedly premature and based on a very limited sample. Until the clinicopathological features of this group of tumors are better defined, we strongly recommend that they be classified according to the scheme listed in Table 11. Only then, will we be able to determine the most beneficial course of therapy.

B. Etiology

Smoking, alcohol abuse, prior irradiation exposure and, possibly, poor oral hygiene, all have been implicated as important risk factors for the development of these tumors (36–39). Studies thus far indicate that the HPV has little, if any, etiological significance (39).

C. Clinical Features

Most patients with SPCC (used here in a generic sense to encompass all of the subtypes in Table 11 because most investigators have not attempted to subclassify these entities) are men (68–99%) in the 50 to 80 year

age group (9,12,13,35,40–45). Occurrence in young patients is unusual. The case of SPCC of the tongue occurring in a four-year-old boy reported by Kessler and Bartley may be the youngest patient with this tumor reported thus far (46).

Although SPCC can arise from any cutaneous or mucosal site in the head and neck, the larynx, especially the true vocal cords and anterior commissure, and esophagus—usually the middle and lower thirds—are among the most common sites. In the oral cavity, the predominant sites, in descending order of frequency, are the lips (particularly the lower lip), tongue, and alveolar ridge-buccal mucosa (40). Most individuals present with hoarseness, a change in quality of the voice, dysphagia, or airway obstruction. Few may even cough up bits of their tumor. Oral cavity tumors, in turn, usually manifest as a swelling with or without pain or a nonhealing ulcer.

D. Pathology

Depending on the series, 70% to 100% of SPCCs of the larynx are polypoid, firm, pink, white, or gray, with a mucosal attachment that varies from a broad base to a thin string-like stalk (27,44,45) (Fig. 63). Sessile or ulceroinfiltrative lesions are less common. In the oral cavity, the distribution between polypoid and ulcerative tumors is about equal. Most are 1 to 6 cm, but in the esophagus, they may reach 12 to 15 cm (47). The surface of the tumor is frequently ulcerated and covered by a shaggy exudate (Fig. 64). As such, biopsies from these areas are often returned by the pathologist as “granulation tissue,” “tissue consistent with pyogenic granuloma,” or as “inflammation with stromal atypia.” The squamous carcinoma tends to be concentrated at the base or stalk of the tumor; therefore, when clinically suspected, all biopsies should include this region (Fig. 64).

Immunohistochemical assays for epithelial markers (cytokeratin, epithelial membrane antigen) and electron microscopy have shown epithelial

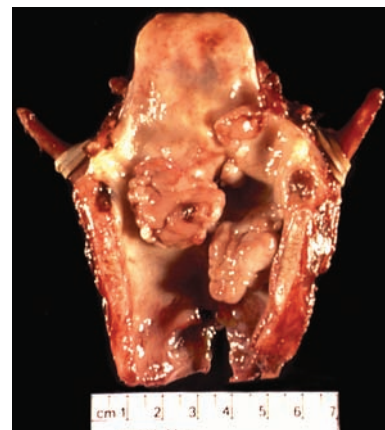


Figure 63. Spindle cell carcinoma of the larynx. Note the characteristic polypoid configuration.

differentiation of the spindle cells in only 40% to 75% of cases (12,13,18,44,45). Approximately 7% to 15% of tumors will also contain heterologous elements, such as malignant osteoid, cartilage, and muscle (12,44,45). This suggests, as noted earlier, that SPCC is not a uniform tumor, but rather, a heterogeneous group of lesions that can be segregated, by routine histology, immunohistochemistry, or electron microscopy, into the four categories shown in Table 11.

Squamous cell carcinomas with a reactive or desmoplastic stroma contain islands of malignant squamous cells associated with a fibrocollagenous stroma that is readily recognized by the pathologist as being benign or, at most, atypical (Fig. 65). The

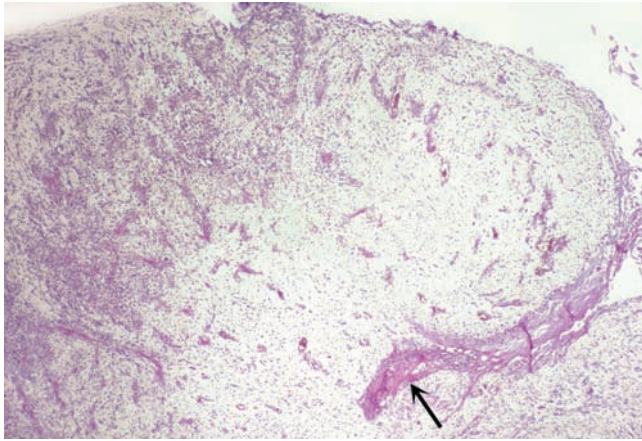


Figure 64. Ulcerated, polypoid spindle cell carcinoma of the true vocal cord. If suspected, biopsies should always be taken from the base of the lesion (*arrow*), rather than the inflammatory surface. This is usually where the most diagnostic portion of the tumor is found (H&E, 20 $\times$).

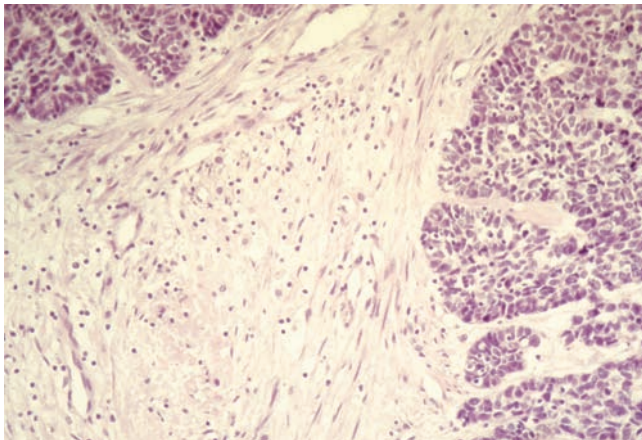


Figure 65. Low-power view of a squamous cell carcinoma with a reactive (desmoplastic) stroma (H&E, 100 $\times$). The spindle (stromal) cells are negative on immunostaining for epithelial markers such as cytokeratin and do not show epithelial differentiation by electron microscopy.

stroma may contain inflammatory cells and increased blood vessels, but the spindle cells (more appropriately fibroblasts or myofibroblasts) show a uniformly negative result for cytokeratin. In addition, the carcinoma is always well demarcated from the stroma.

Spindle cell squamous carcinomas, on the other hand, contain areas of squamous cell carcinoma, either in situ or invasive, and an obviously malignant spindle cell component (Fig. 66). The carcinoma varies from well to poorly differentiated and may be either sharply demarcated from the spindle element, or poorly defined, often appearing to give rise to the spindle cells. The spindle cells usually assume a pattern reminiscent of a fibrosarcoma or a malignant fibrous histiocytoma, yet the cells test positive, either focally or diffusely, for cytokeratin (Fig. 67). At times, especially

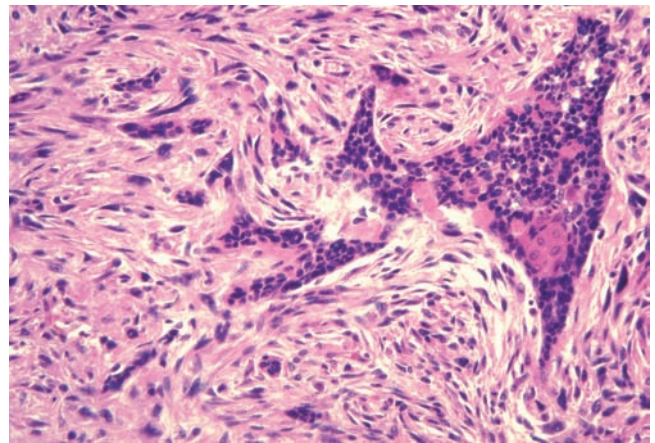


Figure 66. Spindle cell squamous carcinoma. Both epithelial and spindle components appear histologically malignant. Also note that the epithelial cells appear to merge or give rise to some of the spindle cells (H&E, 200 $\times$). See Figure 67.

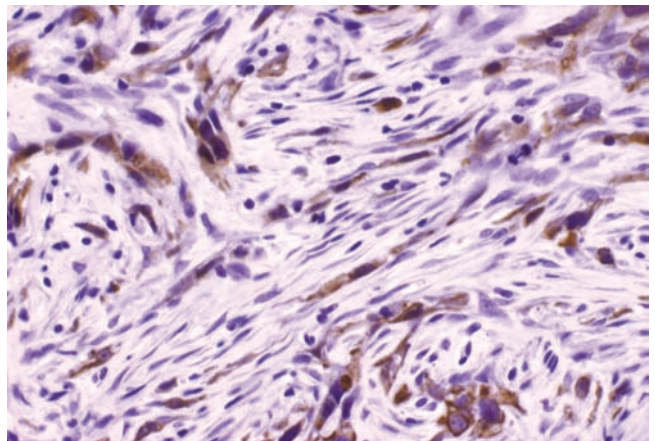


Figure 67. The spindle cells of the tumor shown in Figure 66 resembled a fibrosarcoma on H&E, but were positive for cytokeratin (IHC, AE1/3, 400 $\times$).

on small biopsies, only the spindle component is present, and pathologists may be tempted to diagnose the lesion as a sarcoma. However, because sarcomas are rare in the head and neck, the temptation should be resisted until a spindle cell squamous carcinoma has been excluded by obtaining multiple, deeper histological sections; examining immunostains for cytokeratin; performing electron microscopy; or requesting another biopsy (Fig. 67). Such lesions are often referred to as “monophasic spindle cell carcinomas.” As a general rule, any sarcomatous-appearing lesions adjacent to a mucous membrane in the head and neck, should suggest a SPCC until proved otherwise.

Carcinosarcomas are those tumors composed of a squamous cell carcinoma (rarely other types of carcinomas) intimately associated with a malignant spindle cell component. Foci of osteosarcoma, chondrosarcoma, or rhabdomyosarcoma are not uncommon (Fig. 68). Although the spindle cells are characteristically negative for cytokeratin and fail to show epithelial differentiation on electron microscopy, a few tumors will be encountered in which the spindle cells are focally positive for cytokeratin. In these instances, to qualify as a carcinosarcoma, one must find heterologous elements or demonstrate additional spindle cells that stain positively for nonepithelial markers, such as desmin, myoglobin, or other.

Collision tumors are extremely rare and presumably arise from two simultaneous clones of malignant cells, one epithelial and one mesenchymal that by sheer coincidence arise in adjacent sites, but yet do not intermingle (Figs. 69–71).

When SPCCs disseminate, the metastases most often will show a prominent epithelial pattern, but occasionally both epithelial and spindle cell components will appear and, in a few instances, only the spindle cell element will metastasize (Fig. 72).

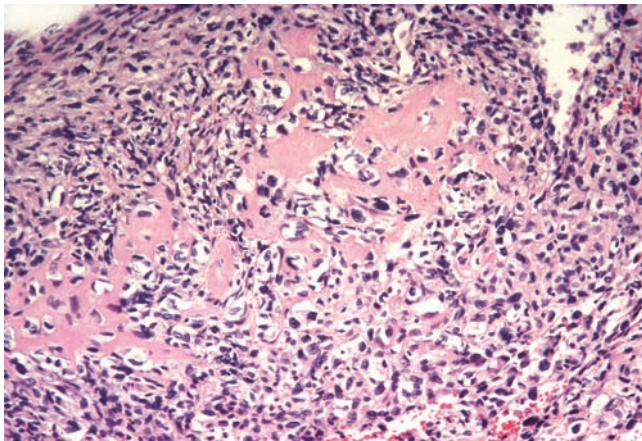


Figure 68. Carcinosarcoma. Focus of osteosarcoma found in a tumor histologically similar to that shown in Figure 67 (H&E, 200×). This combination of findings supports a diagnosis of carcinosarcoma.



Figure 69. Gross appearance of a collision tumor of the pyriform sinus area. This patient had a squamous cell carcinoma of the pyriform sinus treated with surgery and radiation and approximately 12 years later, developed this multinodular tumor composed of squamous cell carcinoma and malignant fibrous histiocytoma. See Figures 70 and 71.

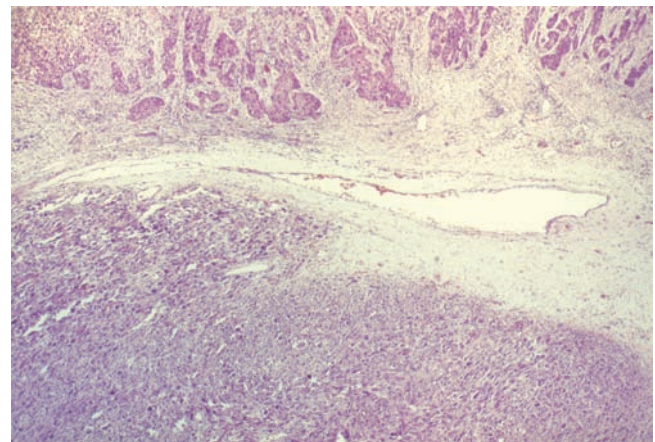


Figure 70. Collision tumor shown in Figure 69. Note the squamous cell carcinoma at top and malignant fibrous histiocytoma at bottom. The two components do not intermingle (H&E, 100×).

E. Immunohistochemistry

In a review of 187 SPCCs of the larynx, Thompson et al. observed that the spindle cell component was positive for at least one epithelial marker in 68% of cases and suggested the use of a screening panel consisting of AE1/3, epithelial membrane antigen (EMA), K1 and K18 (45). More specifically, they observed that 41% of the tumors were positive for K1, 26% for AE1/3, 24% for K18, 15% for K14, 9% for K6, and 7% for K5/6, and 18% for EMA. In contrast to our experience, none was positive for CAM5.2. The

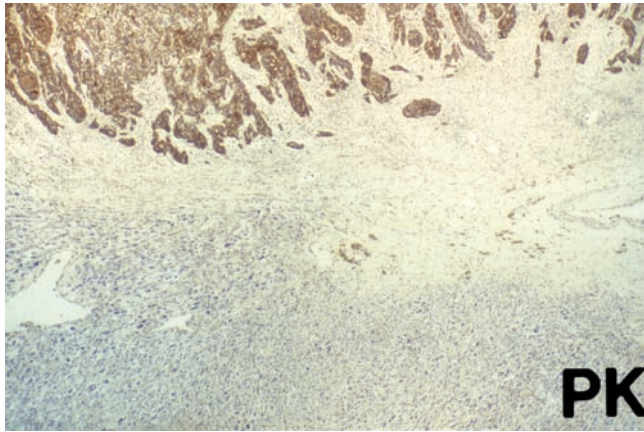


Figure 71. Collision tumor shown in Figures 69 and 70. A cytokeratin stain shows the carcinoma to be positive and the sarcoma negative. Again, note that the tumor components are separate and do not intermingle (IHC, prekeratin, 40 $\times$).

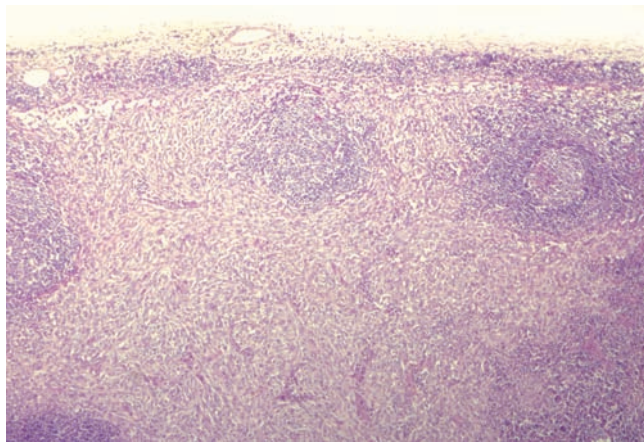


Figure 72. Lymph node in which only the spindle cell component has metastasized (H&E, 100 $\times$).

tumors were also positive for a variety of mesenchymal markers, including vimentin (100% positive), smooth muscle actin (33%), S-100 protein (5%), and desmin (2%).

More recently, p63 has been found to be a useful alternative marker. Lewis et al. observed it to be positive in the spindle cells in 63% of the cases tested (48).

F. Molecular-Genetic Data

Microdissection-based genotypic analysis of the epithelial and mesenchymal components have shown that each exhibits an equivalent pattern of loss of heterozygosity implying that both elements most likely originate from a single (monoclonal) totipotent

cell with disparate phenotypic expression or divergent differentiation (22–29).

Ploidy analyses of SPCCs have shown that the majority (78% of cases) are aneuploid and or tetraploid and that both epithelial and spindle components usually exhibit concordant patterns (44).

G. Differential Diagnosis

Posttraumatic spindle cell nodules, inflammatory myofibroblastic tumors (inflammatory pseudotumors), and radiation fibrosis, must be considered in the differential diagnosis (49–51). A history of trauma; presence of a significant inflammatory component; and lack of atypical mitoses, dysplasia and significant cellular pleomorphism are features of pseudotumors rather than SPCCs. It should be noted that inflammatory myofibroblastic tumors may contain a few keratin-positive cells (myofibroblasts), and should not be misconstrued as evidence to support a diagnosis of SPCC. The fibroblasts associated with radiation are negative for p53 while SPCCs are often positive (52,53).

Attention has already been called to the fact that some SPCCs are monophasic and may masquerade as soft tissue sarcomas, especially since some SPCCs and sarcomas share similar mesenchymal markers (vimentin, smooth muscle actin, etc.) and even keratin expression (especially leiomyosarcomas and synovial sarcomas) (see “Pathology and Immunohistochemistry” above). A p63 stain may be very helpful. SPCCs are often positive (63% of cases) for p63, while sarcomas are almost invariably negative (especially leiomyosarcomas) (48). Amelanotic spindle cell melanoma and spindle cell myoepithelioma may also be included in the differential diagnosis but can usually be excluded by appropriate immunomarkers.

In some small biopsies, a definitive diagnosis cannot be rendered. In this instance, a diagnosis of “malignant spindle cell lesion” is appropriate with a comment that an SPCC, as well as other lesions, should be considered in the differential diagnosis.

H. Treatment and Prognosis

Surgery is the treatment of choice with the extent based on the stage of the disease. Irradiation is generally unrewarding as a primary procedure but may have merit as an adjunct. Whether additional therapy is warranted or prognosis is related to the four subtypes of SPCC listed in Table 11 is unknown since large series of tumors classified accordingly with adequate follow-up are not available. As a result, we are forced to analyze the clinical data pertaining to these tumors collectively. It is of interest, however, to note that there is data indicating that “metaplastic carcinomas” of the breast with absent or minimal invasive carcinomatous component behave more like sarcomas and therefore should probably be treated with sarcoma rather than the usual breast cancer protocols (54). The incidence of cervical lymph node involvement, distant metastasis, and mortality,

Table 12 Spindle Cell Carcinoma: Incidence of Metastasis and Mortality

Author	No. of cases	Site	Cervical lymph node metastasis (%)		Distant metastasis (%)	Mortality (%)
Hyams	39	Larynx and hypopharynx	26		—	40 (mean 1 yr.)
Lambert	116	Larynx and hypopharynx	15	Glottic tumors	5	32 at 3 yr
			30	Supraglottic tumors		
			66	Hypopharyngeal tumors		
Ellis	59	Oral cavity	24		20	55 (mean 1.9 yr.)
Batsakis	111	All sites in head and neck	24		—	35 (usually within 2.5 yr)
Leventon	20	All sites in head and neck	45		—	45
Zarbo	25	All sites in head and neck	32		20	28 (mean 10 mo.)
Berthelet	17	All sites in head and neck	—		—	28 at 2 yr
Thompson	187	Larynx	7		10	32% (mean 3.1 yr.)
Lewis	26	Larynx	9		14	18% (median 6.4 yr.)

without regard to the site or stage of disease, are listed in Table 12. Cervical lymph nodes and lungs are the most frequent sites of dissemination. Following treatment, 20% to 45% of laryngeal SPCCs have developed local recurrences.

Prognosis is related to location, tumor size, depth of invasion, stage of disease, and, to some extent, with gross configuration of the tumor. Small tumors in strategic sites, such as the true vocal cords, are more likely to have a favorable prognosis because of early symptomatology. Tumors of the oral cavity and sinonasal tract tend to be more aggressive. Some reports have indicated that polypoid tumors either do not metastasize or have a more favorable outcome than the flat ulcerative type. While polypoid lesions do, in general, have a better prognosis, they are certainly capable of metastasizing and causing death. Leventon and Evans indicate that the degree of invasion may be the most important factor rather than the gross appearance of the tumor (41). According to them, tumors which invade muscle, minor salivary glands or bone are associated with a poor survival whereas those tumors which are superficial and do not involve these structures have a good survival. Some polypoid tumors, therefore, may exhibit rather deep invasion.

In the extensive review of SPCCs of the larynx by Lambert et al., the three year survival rate was 90% for glottic tumors that were polypoid but only 44% for sessile glottic lesions (35). Prognosis was poor for supraglottic and hypopharyngeal tumors, regardless of pattern of growth. In Ellis and Corio's review of oral cavity tumors, 40% of patients with polypoid tumors and 40% with endophytic lesions succumbed to their disease (40).

Leventon and Evans also indicate that tumors that arise in a site of previous irradiation tend to be more aggressive than those that arise in a nonirradiated

area and that the amount and degree of differentiation of the carcinomatous component are not related to survival or tumor behavior (41). Positive cervical lymph nodes are an ominous finding.

XVI. VERRUCOUS CARCINOMA

A. Introduction

Verrucous carcinoma was first described by Ackerman in 1948 and is often referred to as "Ackerman's tumor" in his honor (1–3). It is defined by the World Health Organization as "a nonmetastasizing variant of well-differentiated squamous cell carcinoma characterized by an exophytic, warty, slowly growing neoplasm with pushing margins (4)."

Although the oral cavity is the most frequent site of origin, 10% to 15% of all VCs occur in the larynx and, in the larynx, 1% to 3% of all carcinomas are of the verrucous type (5–12).

B. Clinical Features

Most arise from the true vocal cords, although in the series of 44 cases reported by Lundgren et al., 27% occurred in the supraglottic larynx (8,13) (Fig. 73). Most individuals have been men (85–95%), averaging 58 to 62 years of age (range 29–83 years) (6,8,14). Hoarseness is the usual presenting symptom. Dysphagia, airway obstruction, and hemoptysis are uncommon.

C. Etiology

The use of tobacco appears to be an important risk factor. Most of the patients described thus far have been smokers. HPV, particularly types 16 and 18 and rarely 6 and 11, have been found in some, but not all,

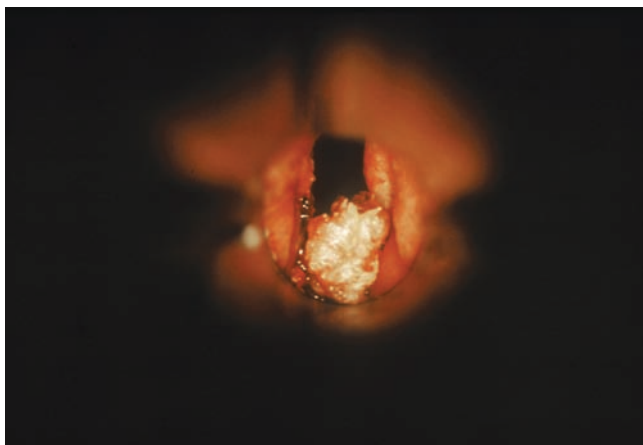


Figure 73. Direct laryngoscopic view of a verrucous carcinoma in region of anterior commissure. Note the exophytic appearance.

VCs (15–19). Whether or not the virus is etiologically linked to VC, however, is uncertain.

D. Pathology

The gross and histological features are identical with those seen in the oral cavity (Figs. 74–76). Hybrid (mixed) tumors composed of areas of both VC and conventional squamous cell carcinoma have also been described in the larynx; however, the frequency of such tumors in the larynx (11% in one study) is

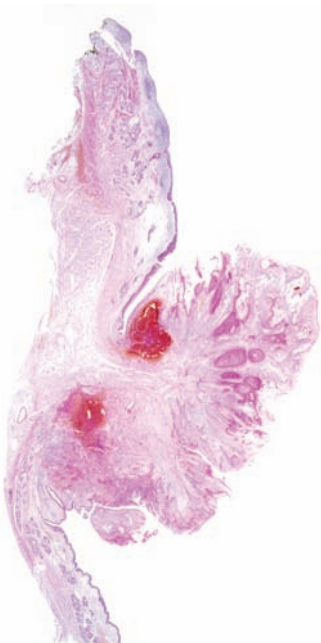


Figure 74. Verrucous carcinoma shown in Figure 73. Note the exophytic, warty growth and the extensive surface keratinization.

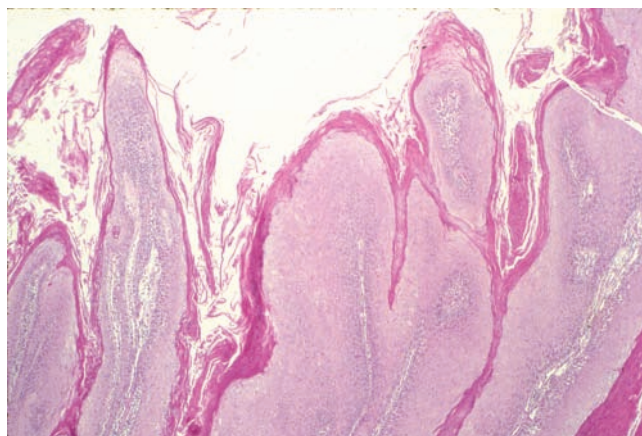


Figure 75. Verrucous carcinoma. Note the papillary surface, prominent keratin layer and absence of keratohyaline granules (H&E, 100 $\times$).

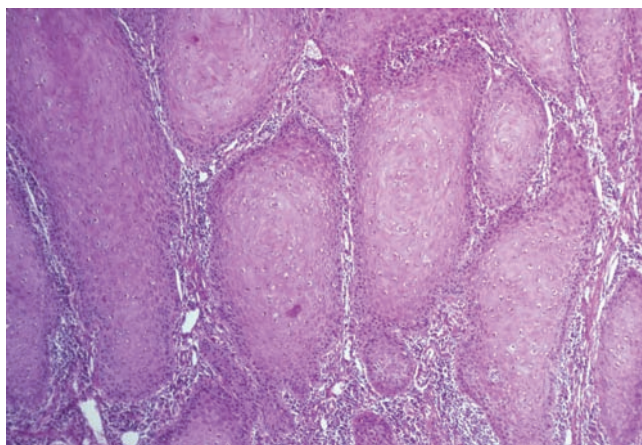


Figure 76. Verrucous carcinoma. The tumor invades as large islands of well-differentiated squamous cells preceded by an inflammatory stromal reaction (H&E, 100 $\times$).

significantly less than the 20% incidence observed in the oral cavity (12,20) (Fig. 77). Nevertheless, it emphasizes the need for thorough microscopic examination of all VCs, because the presence of foci of conventional squamous cell carcinoma in an otherwise typical VC indicates a potential for metastasis.

E. Molecular-Genetic Data

p53 over expression as determined by immunohistochemistry can be found in 40% of VCs, which is similar to other head and neck neoplasms (21).

Sakurai et al. studied C-erbB-3 protein, a growth factor, in a series of verrucous hyperplasia, verrucous carcinoma, and well-differentiated squamous cell carcinoma arising in verrucous carcinoma and observed

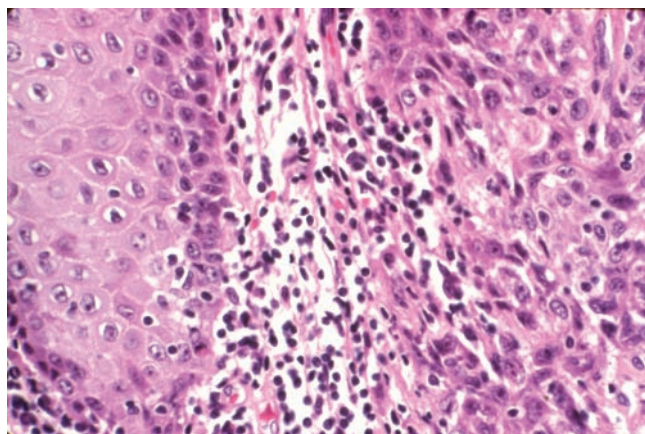


Figure 77. Hybrid verrucous carcinoma. This tumor is composed of both verrucous carcinoma (*left*) and conventional squamous cell carcinoma (*right*). Note the degree of pleomorphism between the tumor components (H&E, 400 $\times$).

a progressive increase in expression. They suggested that this protein might contribute to tumor growth and malignant transformation (22).

Choi et al. indicate that genetic alterations at the short arm of chromosome 9 are early events in carcinogenesis and are commonly shared by the majority of squamous carcinomas of the head and neck, including VC (23). They also observed that less aggressive variants of squamous carcinomas (verrucous, papillary and well-differentiated conventional) had significantly lower loss of heterogeneity (LOH) than the more aggressive types (basaloid, spindle cell, and high grade conventional).

Although some investigators have observed differences in LOH at 4q and 17q between VC and conventional squamous cell carcinoma, these differences were not confirmed in a study that compared VC with only well-differentiated, conventional squamous cell carcinoma (23,24).

F. Differential Diagnosis

The differential diagnosis includes papillary keratosis, verruca vulgaris, and well-differentiated papillary squamous cell carcinoma. Features that are useful in separating these lesions are discussed in sections VIIC, VIII and XVII.

G. Treatment and Prognosis

Although VC may be treated with either surgery or radiation, surgery is more effective (6,8,10,25–28). In a review of 144 VCs of the larynx treated by surgery (vocal cord stripping for T1 lesions, cordectomy or hemilaryngectomy for T2 lesions, and total laryngectomy for T3 and T4 lesions), Hagen et al. noted that 92.4% were cured, 7.6% failed therapy, and 3.5% died of disease (28). In a review of 148 VCs from all head

and neck sites treated with radiation, Ferlito et al. observed 43.2% were cured and 56.8% failed therapy (26). Other studies have also shown a 46 to 57% rate of failure for primary radiation therapy (8,10,28). If a tumor responds at all to radiation, it usually takes one to two months before it disappears (8).

In the past, radiation was rarely used as a therapeutic modality for VC for fear of anaplastic transformation. A critical review of these cases of alleged anaplastic transformation, however, has shown that most were actually conventional squamous carcinomas that were incorrectly labeled as VCs. Current estimates indicate that no more than 5% to 10% of all irradiated VCs will become more aggressive following treatment (8,28,29). Some of these may be examples of unrecognized hybrid carcinomas. Selected patients with VC of the larynx may also be managed with endoscopic resection, with or without laser ablation (7,10,30). However, with this approach, repeated endoscopic resections are often necessary.

Although patients with VCs may have palpable cervical lymph nodes, this is almost invariably due to reactive hyperplasia secondary to an inflammatory response associated with the primary tumor site. A neck dissection is therefore not warranted. VC of the larynx is rarely fatal; death due to disease is 4% (28,29).

XVII. PAPILLARY SQUAMOUS CELL CARCINOMA

A. Introduction

Papillary squamous cell carcinoma (PSCC), strictly defined, is a nonkeratinizing variant of squamous cell carcinoma composed of mitotically-active, basaloid cells arranged in a papillary configuration with delicate fibroblastic cores. It has a favorable prognosis and should be distinguished from a conventional (keratinizing) squamous cell carcinoma with a papillary or exophytic growth (1–14).

B. Etiology

The tumors usually arise *de novo* but in some instances may arise in papillomas associated with recurrent respiratory papillomatosis. HPV types 6,11,16 and 18 have been detected in a few cases (2,3,5,6). Whether this virus has a role in the etiology of PSCC remains unsettled. Smoking and alcohol are also possible risk factors (2).

C. Clinical Features

PSCC may arise from any mucosal site of the upper aerodigestive tract (3). The larynx, however, is one of the most frequent sites. In this location, they are more common in men by a 3:1 ratio and typically occur in patients over the age of 50 years (range 30–74 years) (2). The supraglottic and glottic regions are the preferred sites and, as such, hoarseness and airway compromise are the usual manifestations.

D. Pathology

PSCCs may be localized or diffuse, solitary or multifocal, and in situ or invasive. They have a characteristic papillary surface and contain fibrovascular cores covered by multiple layers of squamous cells with a basaloid appearance (Figs. 78 and 79). Mitoses are frequent, but surface keratinization is characteristically sparse to absent. Some tumors may also contain a few interspersed mucous cells, especially when they involve the laryngeal ventricle.

The tumors often extend over a broad surface area with a “stuck on” appearance, much like papillary

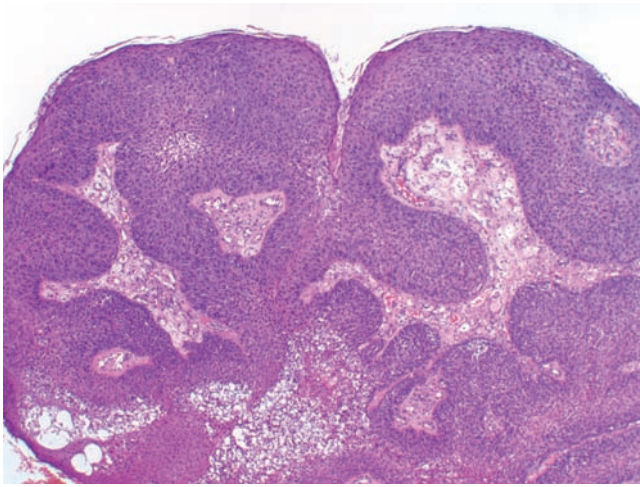


Figure 78. Papillary squamous carcinoma. Note the papillary surface, fibrovascular cores, and lack of surface keratinization (H&E, 20 $\times$).

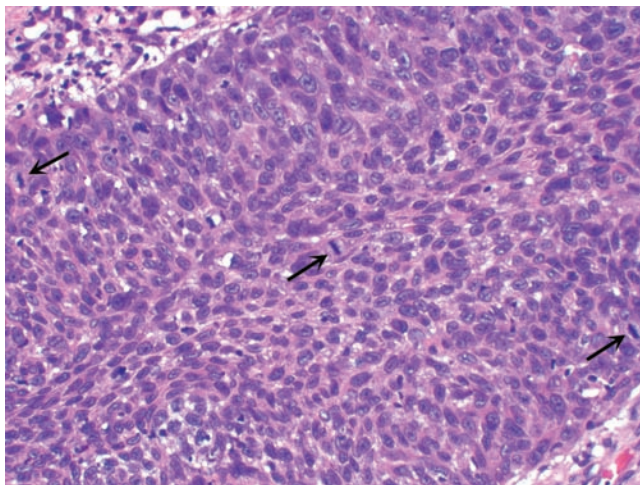


Figure 79. Papillary squamous cell carcinoma. Observe the basaloid cells and frequent mitoses (arrows) throughout all layers. Compare with Figure 80 (H&E, 400 $\times$).

transitional cell carcinoma of the genitourinary tract. Despite their large size, the tumors often remain in situ or exhibit only superficial invasion. Not infrequently, more than one biopsy may be necessary to establish the diagnosis.

Some PSCCs are positive immunohistochemically for p53 and/or show evidence of HPV by in situ hybridization or polymerase chain reaction (3,4).

E. Differential Diagnosis

The two lesions that are most often confused with PSCC are the nonkeratinized papilloma (NKP) associated with HPV-recurrent respiratory papillomatosis and the exophytic squamous cell carcinoma (ESCC) (Figs. 23, 24, and 80). NKPs, especially those that rapidly recur following excision, may show atypia/dysplasia (7). Most often the atypia/dysplasia is in the form of basal cell hyperplasia. Mitoses may be seen but they are normal and limited to the lower half of the epithelium, whereas in PSCC there is full-thickness epithelial disarray and normal and abnormal mitoses are often observed throughout all layers of the epithelium. The clinical history may also be helpful. NKP occurs primarily in children and young adults and is often associated with a prolonged history of recurrent lesions while PSCC frequently occurs ab initio in individuals older than 50 years.

ESCC is a conventional (keratinizing) squamous cell carcinoma but with an exophytic growth. In contrast to the basaloid cells of PSCC, the cells in ESCC are more pleomorphic and often exhibit dyskeratosis (Figs. 79 and 80). The surface of an ESCC also tends to be somewhat keratinized. Mixed lesions with features of both PSCC and ESCC should be classified as an ESCC.

The literature often states that PSCC must also be distinguished from a VC. This should never be an issue. The two lesions do not even remotely resemble

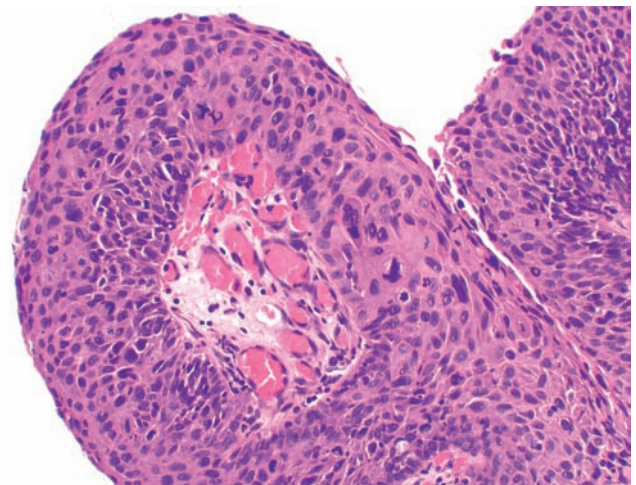


Figure 80. Exophytic squamous cell carcinoma. Note the cells are more keratinized (or squamoid) rather than basaloid (H&E, 400 $\times$).

each other. VC has a heavily keratinized surface and the cells are exceedingly well differentiated with a pink, nonbasaloid appearance free of mitoses. In addition, the rete ridges are bulbous.

F. Treatment and Prognosis

PSCCs, as defined above, are uncommon and therefore no large series are available to evaluate the effectiveness of various therapeutic strategies, which have ranged from biopsy followed by radiation to surgical excision (2). In the larynx, the prognosis is favorable and no doubt relates to the fact that the majority of tumors are either *in situ* or show only superficial invasion. Involvement of regional lymph nodes is uncommon and distant metastasis is exceptional. PSCCs in other sites, especially the sinonasal tract, may be more aggressive.

XVIII. BASALOID SQUAMOUS CELL CARCINOMA

A. Introduction

Basaloid squamous cell carcinoma (BSCC) is an aggressive variant of squamous cell carcinoma that was first described in the head and neck by Wain et al. in 1986 (1). In the upper aerodigestive tract, it occurs primarily at the base of the tongue, hypopharynx and supraglottic larynx but has also been found in the palate, buccal mucosal, floor of mouth, nasopharynx, nasal cavity, and trachea (1–13). It has also been observed in sites below the clavicles, including the lung, esophagus, glans penis, anus, and uterine cervix (14–21).

B. Etiology

As with conventional squamous cell carcinoma, tobacco and alcohol abuse are strong risk factors (2). The Epstein-Barr virus (EBV) has been identified in three patients from Hong Kong with BSCC of the nasopharynx, but has not thus far been found in BSCC in other sites (22). HPV, usually types 16 and 18, has also been detected in some BSCCs, especially those of the glans penis and anus (20,23–26). Whether EBV and HPV are etiologically related to BSCC remains to be determined.

C. Clinical Features

In the head and neck, BSCC occurs primarily in men (82% of all cases) and patients between 27 and 88 years of age (average 63 years) (2). Symptoms vary according to site of origin, but usually include a neck mass, dysphagia, hoarseness, pain in the throat, weight loss, otalgia, and/or hemoptysis.

D. Pathology

The tumors vary between 1 and 6 cm in greatest dimension and are firm, white, or yellow-white with a characteristic gross appearance of central ulceration with prominent submucosal infiltration (Fig. 81). In

fact, because of the submucosal growth, many are clinically thought to be of nonepidermoid origin and are often confused with a minor salivary gland neoplasm or a soft tissue tumor (Fig. 82).

As the name implies, BSCC is composed microscopically of two components: basaloid and squamous cells. The basaloid cells are arranged in smooth-contoured lobules, small clusters, and cords with frequent mitoses and often prominent peripheral palisading

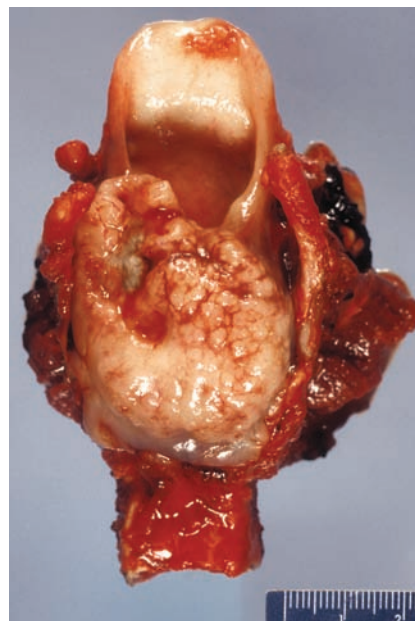


Figure 81. Basaloid squamous cell carcinoma of the postcricoid area. Note the central ulceration and prominent submucosal induration.

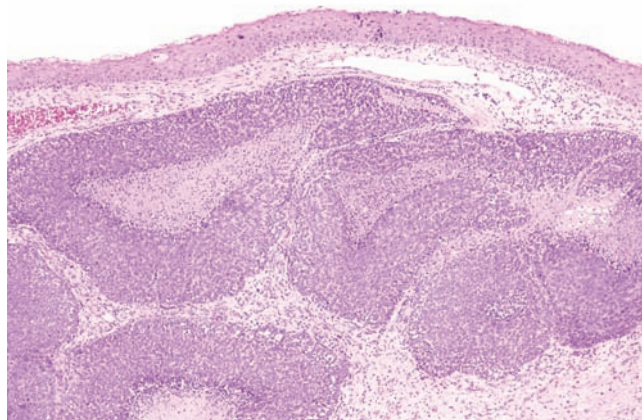


Figure 82. Basaloid squamous cell carcinoma. Smooth contoured lobules with central comedonecrosis are undermining the normal mucosa (H&E, 100×).

of nuclei (Fig. 83). The cells have scant cytoplasm and round to ovoid nuclei that vary from vesicular to hyperchromatic. Nucleoli may or may not be present (Fig. 84). Small cyst-like spaces are occasionally encountered and, rarely, even ductal differentiation is seen (Fig. 83). The spaces may be empty or contain material that resembles mucin, but stains, if at all, only weakly with periodic acid–Schiff (PAS), Alcian blue, or mucicarmine. By electron microscopy, the cyst-like spaces are lined by basal membranes and filled with either loose stellate granules or replicated basal lamina (1). Central ischemic necrosis (comedonecrosis) of the basaloid lobules is characteristic, as well as the deposition of amorphous, eosinophilic material between tumor cells, referred to as hyalinosi (Fig. 85).

At times, the stroma has a myxoid appearance, with basophilic, extracellular connective tissue mucin.

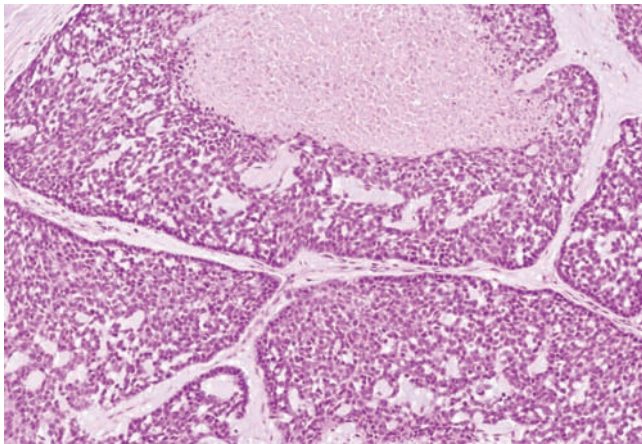


Figure 83. Basaloid squamous cell carcinoma. Smooth, contoured lobules of basaloid cells. Note the central necrosis, peripheral palisading of nuclei and small cyst-like spaces (H&E, 200 $\times$).

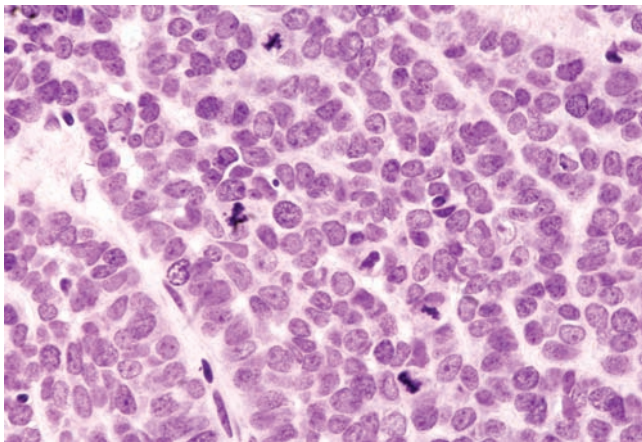


Figure 84. Basaloid squamous cell carcinoma. Note the basaloid cells with round nuclei and frequent mitoses (H&E, 400 $\times$).

In about 5% of cases, the epithelial component will assume a spindle cell configuration, similar to that seen in SPCC (27,28). A case of BSQC associated with a squamous cell carcinoma and rhabdomyosarcoma (carcinosarcoma) has also been described (29).

Although basaloid cells predominate, a definable element of squamous cell carcinoma should be present to make the diagnosis with confidence. The squamous component may be in situ or invasive and is typically well to moderately differentiated (Fig. 86). If there is

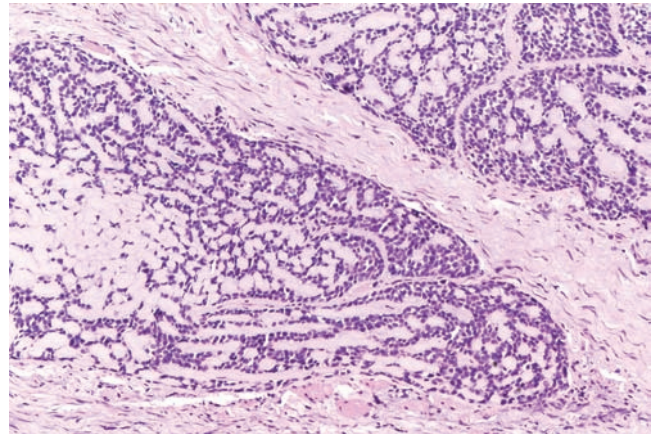


Figure 85. Basaloid squamous cell carcinoma. Cords of basaloid cells separated by eosinophilic hyaline material referred to as hyalinosi (H&E, 100 $\times$).

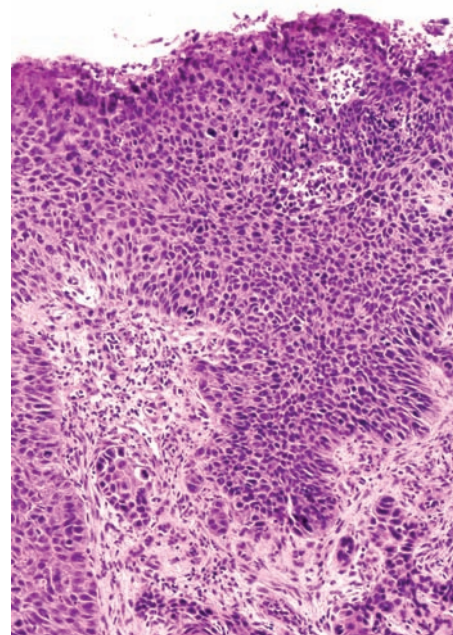


Figure 86. Basaloid squamous cell carcinoma showing a surface component of invasive squamous cell carcinoma (H&E, 100 $\times$).

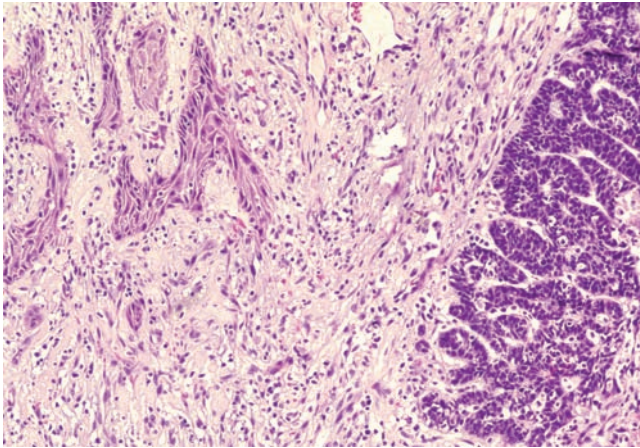


Figure 87. Low magnification of basaloid squamous cell carcinoma showing separate areas of basaloid (*right*) and squamous cells (*left*) in the same area (H&E, 200×).

extensive surface ulceration, only dysplastic changes may be seen in the marginal, intact epithelium. Some of the basaloid islands may also exhibit squamous differentiation and, when this occurs, the transition between the two components may be abrupt or show a zone of transition (Fig. 87).

Some have observed that BSCC often exhibits a multifocal origin from the overlying mucosa and a marked tendency for perineural invasion (7,8); others have not (2,15).

Metastases to regional lymph nodes may be composed of basaloid, squamous, or both components. In general, the basaloid component predominates (2).

E. Immunohistochemistry

The immunoprofile and range of positivity of each stain is given in Table 13 (6,10,18,25,30–36).

F. Electron Microscopy

Ultrastructurally, the basaloid cells contain desmosomes, rare tonofilaments, and free ribosomes, but few other organelles. Neurosecretory granules, myofilaments, and secretory granules are absent (1).

G. Differential Diagnosis

Because of its dual composition, it may be difficult, or even impossible, to establish the diagnosis of BSCC on small biopsies. For the most part, the differential diagnosis revolves around adenoid cystic carcinoma (ACC), small cell neuroendocrine carcinoma (SCNEC) and adenosquamous carcinoma (ASC). Features that are helpful in distinguishing ACC and SCNEC from BSCC are shown in Tables 14 and 15. Clinical features are also potentially helpful in separating BSCC from ACC. ACCs are rarely associated with positive cervical lymph nodes, whereas this is a

Table 13 Immunoprofile of Basaloid Squamous Cell Carcinoma

Stain	% positive
AE1/3	79–100
CK7	71
CK20	7
CAM5.2	55–86
34BE12	86–100
Epithelial membrane antigen	83–100
P63	82–100
Calretinin	45
Carcinoembryonic antigen	29–53
C-Kit	50
Thyroid transcription factor	0
S-100 protein	39–100
Vimentin	0–57
Desmin	0
Muscle specific actin	0–50
Smooth muscle actin	9
Synaptophysin	0–4
Chromogranin	0
Neuron specific enolase	13–75
p53	67–82

Source: Based on Refs. 6, 10, 18, 25, 30–37.

Table 14 Basaloid Squamous Cell Carcinoma Vs. Adenoid Cystic Carcinoma

Features	BSCC	ACC
Lymph nodes	+	–
Cribriform pattern	focal	Often prominent
Nuclei	Hyperchromatic to vesicular, round	dark, angulated
Nucleoli	+/-	–
Mitoses	+	+/-
Squamous carcinoma	+	–
Perineural invasion	Rare	Frequent
Comedonecrosis	Prominent	Rare
Myoepithelial cells ^a	–	+
p53	+	–
Ki-67	High	Low
S-100	focal	Diffuse
C-kit	+/-	+
P63	Diffuse, basaloid, and squamous cells	Myoepithelial cells only

^aAlthough in our experience myoepithelial cells are usually not seen in BSCC, a recent abstract indicates that myoepithelial cells may be seen in some BSCCs (37).

Abbreviation: BSCC, basaloid squamous cell carcinoma; ACC, adenoid cystic carcinoma.

common finding in BSCC. In addition, the larynx and hypopharynx are relatively uncommon sites of origin for ACC.

H. Treatment and Prognosis

BSCC is an aggressive tumor. Raslan et al. reviewed 90 patients and observed that 64% had positive cervical lymph nodes and 44% distant metastases (lungs, liver, bones, brain, and skin) sometime during the course of their disease (2). Thirty-eight percent of the patients died of disease at a median follow-up of 17 months.

Whether BSCC is more aggressive than conventional squamous cell carcinoma is controversial

Table 15 Basaloid Squamous Cell Carcinoma Vs. Small Cell Neuroendocrine Carcinoma

Feature	BSCC	SCNEC
Growth	lobular	diffuse
Spindle cells	–	+
Nuclear molding	–	+
Nucleoli	+/-	–
Hyalinosis	+	–
Stromal mucin	+	–
Cyst-like areas	+	–
Peripheral palisading	+	–
In situ or invasive squamous cell carcinoma	+	–
Synaptophysin, chromogranin, or Leu-7	–	+/-
34BE12 (keratin)	+	–
Thyroid transcription factor	–	+/-
Inclusion body-cytokeratin positivity	–	+/-
Neurosecretory granules on EM	–	+/-

Abbreviations: EM, electron microscopy; BSCC, basaloid squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma.

(8,9,11–13). The general consensus, however, is that when the two tumors are matched for anatomic site, stage, and treatment the prognosis is similar.

Surgery with regional lymphadenectomy and postoperative radiation is the treatment of choice. Because of the high incidence of distant metastases, adjuvant chemotherapy may also be warranted.

Whether or not determination of the DNA content of the tumor offers prognostic significance is controversial. Luna et al. studied nine BSCCs and found that five were aneuploid and four were diploid. Three of the four patients with diploid carcinomas died with distant metastases from 11 to 20 months after diagnosis whereas two of the five with aneuploid tumors died of their disease at 36 and 43 months (8). They concluded that patients with aneuploid BSCC had a better mean survival time (39.5 months) than those with diploid tumors (16.3 months). Raslan et al. studied 10 BSCC and found 6 to be diploid and 4 aneuploid (2). They concluded that tumor ploidy, as determined by flow cytometry, provided no additional prognostic information beyond that supplied by routine histological evaluation.

Seidman et al. indicate that BSCC may be associated with a high incidence of second primary tumors, particularly in the upper gastrointestinal tract and larynx (38). Of six patients with BSCC that had additional primary tumors reviewed by Raslan et al., the second tumor was found in the distal esophagus (small cell carcinoma), soft palate (squamous cell carcinoma), left arytenoid (squamous cell carcinoma), nasopharynx (nasopharyngeal carcinoma), and prostate and colon (one patient had adenocarcinoma in both of these sites (2,3,6,39). The sixth patient had chronic lymphocytic leukemia (6).

XIX. ADENOSQUAMOUS CARCINOMA

A. Introduction

ASC is an uncommon, aggressive malignant tumor that was first described in the head and neck by

Gerughty et al. in 1968 (1). Originally thought to be a type of salivary tumor, it is now established that this is a distinct variant of squamous carcinoma characterized by a dual composition of both squamous and glandular components (2–7).

B. Etiology

As in conventional squamous cell carcinomas, alcohol and tobacco abuse appear to be important risk factors for ASC. Siar and Ng have also described a case that may have been related to prior radiation exposure (8).

C. Clinical Features

ASC is more common in males by a ratio of 4:1 and occurs over a broad age (34–81 years) with an average of 61 years (6). The larynx is the most common site, accounting for 45% of all cases in the upper aerodigestive tract. In a review of 26 tumors of the larynx, Keelawat et al. noted that 46% were supraglottic, 19% transglottic, 15% glottic, 4% subglottic and in 15% the site was unknown (6). Symptoms vary according to site, but usually include airway compromise, hoarseness, sensation of a foreign body in the throat, and/or dysphagia.

D. Pathology

The tumors are grossly indistinguishable from ordinary squamous cell carcinoma and range from 1 to 6.5 cm. Each is composed of squamous and glandular foci in varying proportions, with the former usually predominating. The squamous carcinoma is seen most often in the central part of the tumor originating from a dysplastic mucosa that may be either intact or ulcerated. The adenocarcinoma, in turn, is most often observed in the deeper part of the tumor.

The two carcinomas range from well to poorly differentiated and are typically separate and distinct but occasionally intermingled (Fig. 88). A mucicarmine

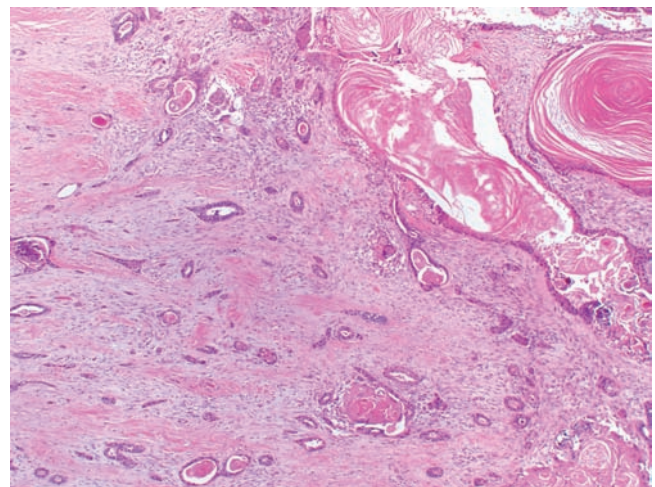


Figure 88. Adenosquamous carcinoma. Note the squamous component in the upper right corner (H&E, 100×).

stain shows, in most cases, luminal and intracellular mucus in the glandular component while keratin pearls and dyskeratotic cells may be seen in the squamous areas. Perineural invasion is also quite common.

Metastases are frequent and, while either component may disseminate either alone or in combination, the squamous carcinoma is usually dominant (6).

E. Immunohistochemistry

The adenocarcinoma is positive for CEA (92% of cases), CK7 (75%), and CAM 5.2 (58%) while the squamous carcinoma is either negative or focally reactive for these markers (7). The high molecular weight cytokeratin 34BE12 is positive in both and CK20 negative. Most are also aneuploid and positive for p53 (7).

F. Differential Diagnosis

Because of its biphasic character the diagnosis of ASC may not be apparent on small biopsies. Often the diagnosis can only be established after the entire lesion has been resected and thoroughly evaluated microscopically. The differential diagnosis includes mucoepidermoid carcinoma, acantholytic (pseudo-glandular) squamous cell carcinoma, basaloid squamous cell carcinoma, and conventional squamous cell carcinoma infiltrating nontumorous salivary and/or mucoserous glands.

The distinction between ASC and mucoepidermoid carcinoma (MEC) is more than academic. The 5-year survival rate for ASC is 13% to 20% compared with 92%, 63%, and 27%, respectively, for low-, intermediate-, and high-grade MEC (9). ASC, as previously described, contains separate areas of adenocarcinoma and squamous cell carcinoma as well as foci where the two components commingle and also exhibits dysplastic-carcinomatous changes in the overlying surface (mucosal) epithelium. In contrast, the glandular and squamous elements in MEC are typically inseparable, and there are no abnormalities of the surface epithelium. Nuclear pleomorphism, high mitotic activity, necrosis, dyskeratotic cells, and keratin pearls are common in ASC but rarely seen in MEC. MEC, in turn, often contains multiple cell types, including mucous, intermediate, clear, and epidermoid cells.

As a result of acantholysis, spaces are created in acantholytic squamous cell carcinoma that be mistaken for true glands and thus cause confusion with ASC. In contrast to ASC, the gland-like spaces in acantholytic squamous cell carcinoma are negative for mucin and carcinoembryonic antigen.

Basaloid squamous cell carcinoma (BSCC) may also be confused with ASC. Both neoplasms exhibit areas of squamous differentiation and duct formation and contain small cysts filled with material staining positive with PAS and/or Alcian blue. However, in BSCC the tumor is composed of large, round, solid clusters of basaloid cells often with central comedonecrosis. Such areas are not seen in ASC. Also unlike ASC, which contains separate foci of adenocarcinoma and squamous cell carcinoma, the ducts in BSCC, if

seen at all, are an integral component of the basaloid component.

Conventional squamous cell carcinoma invading and/or entrapping nontumorous mucoserous glands may also be confused with ASC, especially on small biopsies. Retention of the normal lobular architecture of the mucoserous glands and the lack of any significant cytologic atypia of the glands should always suggest this possibility. Moreover, in true ASC one should see, if the specimen is large enough, one or more separate foci of unequivocal adenocarcinoma.

G. Treatment and Prognosis

Treatment varies according to site and stage of disease, but usually necessitates some form of laryngectomy and neck dissection and possible supplemental radiation (6,10). In a review of 58 ASCs from all sites in the head and neck, Keelawat et al. observed that 47% of patients experienced local recurrences, 65% developed lymph node metastases and 23% had distant dissemination (especially to the lung), with a 5-year determinant survival rate of 13% (6). If only ASCs of the larynx are considered, Fujino et al. in a review of 20 cases, observed that at presentation 25% of patients had cervical lymph node involvement and 5% distant metastases. Following treatment, 55% of the patients experiences local recurrences and another 15% developed systematic metastases. The 5-year survival rate was only 22% (4).

XX. ACANTHOLYTIC SQUAMOUS CELL CARCINOMA

A. Introduction

Acantholytic squamous cell carcinoma (ALSCC) is the term sanctioned by the World Health Organization to described an uncommon variant of squamous cell carcinoma characterized by acantholysis of tumor cells creating a false appearance of glandular differentiation (1). Adenoid squamous cell carcinoma is a popular synonym but its usage often results in confusion with adenosquamous carcinoma. Other terms that have been used to described this tumor include pseudoglandular squamous cell carcinoma, squamous cell carcinoma with gland-like features, adenoacanthoma, and pseudovascular squamous cell carcinoma.

The tumor most often occurs on the sun-exposed skin of the head and neck, including the vermilion border of the lips. Other than the lips, mucosal sites of origin are exceptional and have included the tongue, gingiva, floor of mouth, nasopharynx, hypopharynx and larynx (2–12).

B. Etiology

Prolonged sun exposure appears to be an important etiologic factor for those tumors involving the skin and lips, while prior radiation exposure might have a role in the origin of some mucosal lesions (4,5). As in

conventional mucosal squamous carcinoma, smoking and alcohol abuse are also likely contributors.

C. Clinical Features

ALSCCs are more common in males and typically occur in patients 40 to 70 years of age.

D. Pathology

The tumors may be nodular, exophytic or indurated, often with an ulcerative or "keratotic" surface. They rarely exceed four centimeters.

The acantholysis is commonly seen as a focal change in a background of conventional squamous cell carcinoma but in a few instances, the entire tumor may show this feature. The acantholysis results in tumor nests with a gland-like appearance lined by one or more layers of squamous cells (Fig. 89). The spaces may appear empty, contain acantholytic or dyskeratosis cells, or cellular debris. Clear or spindle cells may also be observed. The stroma is often desmoplastic and inflamed. At times, the acantholysis may create anastomosing spaces and channels mimicking an angiosarcoma (3).

The gland-like areas are devoid of both luminal and intracellular mucin and by electron microscopy exhibit hemidesmosomes and tonofilaments but no glandular features thus supporting the squamous derivation (5,10)

E. Differential Diagnosis

The differential diagnosis includes adenosquamous carcinoma, mucoepidermoid carcinoma and, possibly, angiosarcoma. Features important is separating the first two tumors have already been covered (see

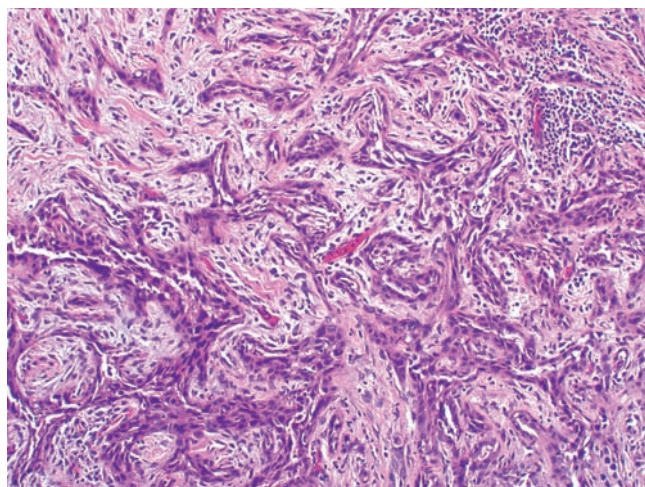


Figure 89. Acantholytic squamous cell carcinoma. Acantholysis of tumor cells creates a pseudoglandular appearance (H&E, 200×).

"Differential Diagnosis" under Adenosquamous Carcinoma above). The pseudovascular ALSCC can be distinguished from an angiosarcoma by immunohistochemistry. Pseudovascular ALSCC is positive for cytokeratin and negative for vascular markers (3).

F. Treatment and Prognosis

There are no large series of ALSCCs of the larynx for evaluation. In fact, the largest series of mucosal ALSCCs deal primarily with those of the lip (8,12). In a review of 26 cases (21 lip, 2 tongue, 1 maxillary gingiva, 1 floor of mouth and 1 unnamed site), Jones et al. observed that 11.5% of patients had died of disease, 77% were free of disease at follow-up ranging from 2 to 72 months and 11.5% had no follow-up. All three of the patients who died of disease had tumors involving the tongue and gingiva. Until proven otherwise, we recommend that all patients with mucosal ALSCCs be treated according to guidelines used in the management of similarly staged conventional squamous cell carcinomas.

XXI. LYMPHOEPITHELIAL CARCINOMA

A. Introduction

Tumors morphologically similar to the undifferentiated type of nasopharyngeal carcinoma can, in rare instances, occur in the larynx and hypopharynx. Such tumors have been referred to as lymphoepithelial carcinoma, lymphoepithelial-like carcinoma, lymphoepithelioma, undifferentiated carcinoma with lymphoid stroma, and undifferentiated carcinoma of nasopharyngeal type. Of these various terms, lymphoepithelial carcinoma (LEC) has emerged as the most preferred (1).

Lymphoepithelial carcinoma of the larynx and hypopharynx is an extremely rare neoplasm. Ferlito identified only 1 case (0.05%) among 2052 malignant neoplasms of the larynx and hypopharynx on file at the University of Padua, and Micheau et al. observed only 3 LECs (0.2%) among 1350 laryngeal carcinomas at the Institut Gustave-Roussy (2,3).

B. Etiology

Although the undifferentiated type of nasopharyngeal carcinoma is characteristically associated with the Epstein-Barr virus (EBV), LEC of the larynx and hypopharynx is only infrequently associated with this virus. In a review of 16 cases that were specifically evaluated for the presence of EBV, only 4 (25%) were positive (4).

Some patients have also been heavy smokers and/or consumers of alcoholic beverages. These may be additional risk factors.

C. Clinical Features

LEC of the larynx and hypopharynx occurs in patients averaging 62 years of age (range 40–82) and is 3 to 6

times more common in men (4,5). In a review of 23 cases, MacMillan et al. noted that 52% arose in the larynx, 43% in the pyriform sinus, and 4% in the trachea (5). Of those occurring in the larynx, two-thirds were of supraglottic origin.

The most common presenting manifestations are hoarseness, followed by a neck mass, sore throat, dysphagia and episodic hemoptysis.

D. Pathology

The tumors have ranged in size from 0.8 to 4.5 cm (mean 2.5 cm) and are histologically identical with the undifferentiated type of nasopharyngeal carcinoma. As such, they are composed of single, small aggregates, or large syncytial masses of cells associated with a prominent component of lymphocytes. The tumor cells have large, round, vesicular nuclei and prominent nucleoli and, on immunostaining, are positive for cytokeratin (Fig. 90). In some instances, the tumor cells may show focal, rather abrupt, squamous differentiation or keratinization. In about half the cases, there is a component of squamous cell carcinoma that accounts for 10% to 75% of the entire tumor. The overlying epithelium may show carcinoma-in situ (5).

E. Treatment and Prognosis

Treatment has ranged from biopsy and subsequent radiation to some form of laryngectomy or pharyngectomy and neck dissection. Approximately 75% of patients either have or will develop positive cervical lymph nodes and 25% to 30% will experience distant metastases (lung, liver, bone, skin and mediastinal and retroperitoneal lymph nodes (4,5). Local recurrence following initial therapy has been recorded in 10% of patients, and at least 25% to 30% have died of

disease after a mean interval of 32 months (range 9–75 months) (4,5).

The frequent occurrence of distant metastases would seem to warrant consideration of adjuvant chemotherapy.

XXII. GIANT CELL CARCINOMA

A. Introduction

Giant cell carcinoma (GCC) of the larynx has been defined by World Health Organization (WHO) as “an undifferentiated carcinoma containing many bizarre multinucleated cells. The tumor cells have abundant eosinophilic cytoplasm that may contain neutrophil leukocytes or cell debris. There is no evidence of squamous or glandular differentiation by light microscopy” (1). Therefore, it is, morphologically identical with the giant cell carcinoma of the lung (2–5).

B. Clinical Features

Giant cell carcinomas of the larynx are exceptionally rare neoplasms. Ferlito et al. identified only four cases among a very large series of laryngeal carcinomas on file at the University of Padua (6). These tumors occurred in four men, aged 56 to 64 years. All were smokers, predominantly of cigarettes, and three consumed alcoholic beverages in moderation. Dyspnea and dysphagia were the most common presenting symptoms.

The tumors occurred in all areas of the larynx, with no specific preferential site. One was subglottic, one involved the right vocal cord and ventricle, one encompassed the vocal cords and subglottis, and one originated in the area of the epiglottis and aryepiglottic fold.

C. Pathology

The tumors are grossly indistinguishable from ordinary squamous cell carcinoma. They have ranged in size from a “small plum” to 2.0 cm and, on cross section, are usually white, hemorrhagic, and necrotic (6).

The histological hallmark of the tumor is the presence of numerous, noncohesive, bizarre giant cells that contain prominent, frequently multiple, nuclei. The cytoplasm is abundant, eosinophilic, sometimes vacuolated, and often contains neutrophils, or cellular debris. The vacuoles may or may not stain for mucin. The tumor, in addition, contains a background population of smaller anaplastic tumor cells, red blood cells, neutrophils, and frequent abnormal mitotic figures. The cells are positive for cytokeratin and, occasionally, carcinoembryonic antigen (5).

The GCC may exist in a pure (as just described) or mixed form, the latter in association with a squamous cell carcinoma, adenocarcinoma, or SPCC. Because of these mixed forms, some have questioned whether GCC is indeed a specific entity and have proposed, at least in the lung, that such mixed tumors should be designated as “pleomorphic carcinomas” (4).

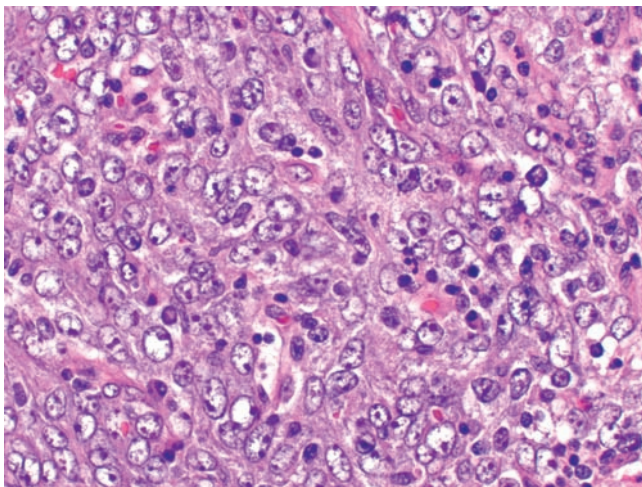


Figure 90. Lymphoepithelial carcinoma of the larynx. Syncytial arrangement of tumor cells composed of round, clear nuclei, prominent nucleoli, and sparse cytoplasm. Lymphocytes permeate the tumor (H&E, 400×).

D. Electron Microscopy

Ultrastructurally, GCC are characterized by abundant mitochondria, concentric whirls of tonofilament-like fibrils, aggregates of centrioles, occasional basement membranes, and cellular junctions (2). Ultrastructural studies further indicate that the neutrophils seen in the cytoplasm of the giant cells enter the cells by emperipolesis, rather than by phagocytosis (2).

E. Differential Diagnosis

The differential diagnosis includes squamous cell carcinoma and adenocarcinoma with foci of giant cells, SPCC, rhabdomyosarcoma, giant cell tumor, and malignant fibrous histiocytoma.

If one rigorously applies the WHO definition for GCC, the presence of any squamous or glandular differentiation is sufficient to exclude its diagnosis. Others, however, indicate that the quantity of giant cells in the tumor is important. To qualify as a GCC, various authors state that the giant cells must compose 10,30,40, or even 55% of the total volume of the tumor (4,5,7). Normally, if giant cells are seen at all in squamous cell carcinoma or adenocarcinoma, they are only focally prominent and not spread diffusely throughout the tumor. The presence of neutrophils in the cytoplasm of the giant cells should also suggest a GCC.

SPCC of the larynx may occasionally contain giant cells and express cytokeratin positivity. It can, however, be distinguished from GCC by the lack of extensive giant cells throughout the lesion, and the absence of neutrophils within the cytoplasm of the giant cells.

GCC can be differentiated from rhabdomyosarcoma by the lack of cross-striations and the use of immunostains for myoglobin or desmin. Giant cell tumors, similar to those of bone, can also occur in the larynx (8). They are, however, easily separated from GCC by their lack of pleomorphism and that, in contrast to GCC, they are negative for cytokeratin. Malignant fibrous histiocytoma, likewise, is also negative for cytokeratin.

F. Treatment and Prognosis

Of the four patients with GCC of the larynx reported by Ferlito et al., three developed metastases to cervical lymph nodes and three died of their disease 4, 6, and 13 months post therapy (6). The fourth patient was reported to be alive and well six years later.

The propensity for cervical lymph nodes metastases suggests the need for either a partial or total laryngectomy and some form of neck dissection. The role of irradiation and chemotherapy remains largely untested.

XXIII. NEUROENDOCRINE TUMORS

A. Introduction

Neuroendocrine tumors of the larynx are a heterogeneous group of neoplasms that range from rather bland to highly malignant. Numerous terms, some

Table 16 Classification of Neuroendocrine Tumors of the Larynx

Terminology	Synonyms
1. Typical carcinoid	Carcinoid, well-differentiated (Grade I) neuroendocrine carcinoma
2. Atypical carcinoid	Malignant carcinoid, moderately differentiated (Grade II) neuroendocrine carcinoma
3. Small cell neuroendocrine carcinoma	Small cell carcinoma neuroendocrine type, poorly differentiated (Grade III) neuroendocrine carcinoma, oat cell carcinoma, small cell carcinoma, anaplastic small cell carcinoma, small cell undifferentiated carcinoma
4. Large cell neuroendocrine carcinoma	Poorly differentiated (Grade III) neuroendocrine carcinoma
5. Combined neuroendocrine carcinoma (small cell neuroendocrine carcinoma with squamous cell carcinoma of adenocarcinoma)	Composite small cell carcinoma, composite neuroendocrine carcinoma
6. Paraganglioma A. Benign B. Malignant	Non-chromaffin paraganglioma, glomus tumor

confusing, have been applied to these tumors. For consistency, we have basically adopted the nomenclature proposed by the World Health Organization for those of the lung and larynx (Table 16) (1,2). The more common synonyms are also listed.

As a group, they are uncommon in the larynx with only about 500 cases recorded in the literature as of 1998 (3). The atypical carcinoid is the most frequent, constituting 54% of neuroendocrine tumors of the larynx, followed by small cell neuroendocrine carcinoma (34%), paraganglioma (9%) and typical carcinoid (3%) (3–7).

Cells histochemically similar to, if not identical with, Kultschitzky cells of the bronchi have been identified in the larynx (8,9). These, as well as pleuripotential, endodermal stem cells, are the putative cells of origin for the carcinoid, atypical carcinoid, and small cell neuroendocrine carcinoma (6,10). Paragangliomas of the larynx, in turn, are thought to arise from paraganglionic tissue normally found in the larynx (7).

B. Typical Carcinoid

Clinical Features

The typical carcinoid (TC) is the least common of the neuroendocrine tumors of the larynx with only 42 cases recorded as of 2004 (11). They are three to nine times more common in men and occur in patients averaging about 58 to 64 years of age (range 45–80) (4–11). Most (83%) occur in the supraglottic larynx in the vicinity of the aryepiglottic fold, arytenoids or false vocal cord.

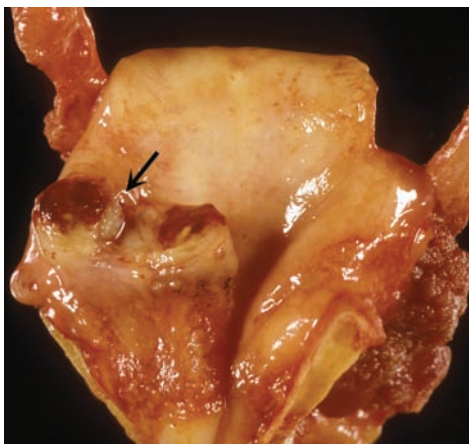


Figure 91. Supraglottic laryngectomy specimen opened posteriorly revealing a submucosal, hemorrhagic, typical carcinoid of the left aryepiglottic fold (arrow). *Source:* From Sec. XXIII, Ref. 12.

Symptoms, ranging from three weeks to four years in duration, include dysphagia, hoarseness, and sore throat. Smoking appears to be a risk factor.

Pathology

The TCs range from 0.5 to 3 cm (average 1.6 cm) in greatest dimension and present as submucosal nodules or polypoid masses (4) (Fig. 91). Microscopically, they are composed of small uniform cells that grow in cords, small nests, large sheets, glands, or pseudorosettes (Fig. 92). The cells have cytoplasm that varies from clear to eosinophilic. The nuclei are usually round, occasionally spindle, and have finely stippled or dense chromatin (Figs. 93 and 94). Nucleoli and mitoses are sparse to absent (less than 2 mitoses per 10 high power fields), and necrosis and pleomorphism

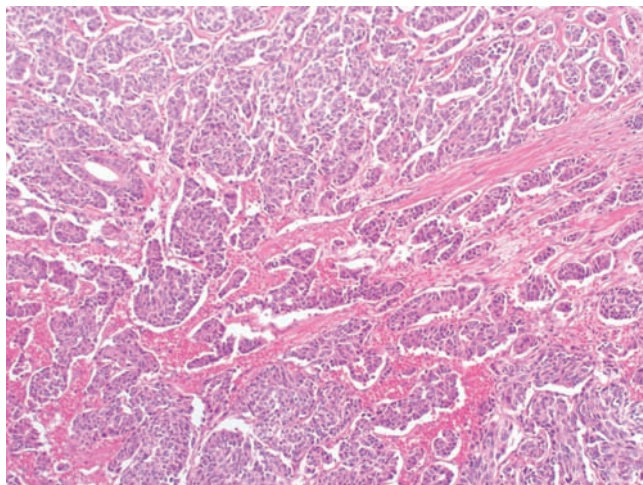


Figure 92. Typical carcinoid composed of small cords and clusters of cells (H&E, 100 $\times$).

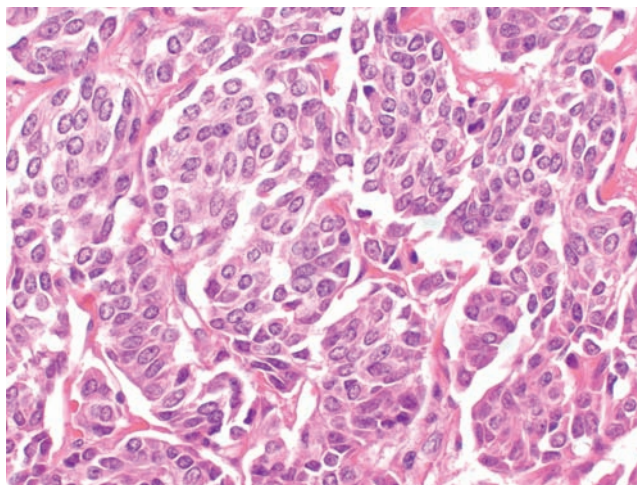


Figure 93. Typical carcinoid composed of small cells with uniform, round nuclei. Note the absence of nucleoli, mitoses, and necrosis. Compare with Figure 97. (H&E, 400 $\times$).

are not seen (1,2,10,12). The stroma is highly vascular and, often, focally fibrotic or hyalinized.

In a few instances, carcinoids, either typical or atypical, may appear either oncocytic or oncocytoid (13,14). Such tumors have abundant eosinophilic cytoplasm and neurosecretory granules. The distinction between these two lesions depends on the presence (oncocytic) or absence (oncocytoid) of mitochondrial hyperplasia on ultrastructural examination. A few may even contain mucin and, exceptionally, even amyloid.

Immunohistochemistry

TCs are positive for cytokeratin, epithelial membrane antigen, carcinoembryonic antigen, synaptophysin, chromogranin, neuron specific enolase, and protein

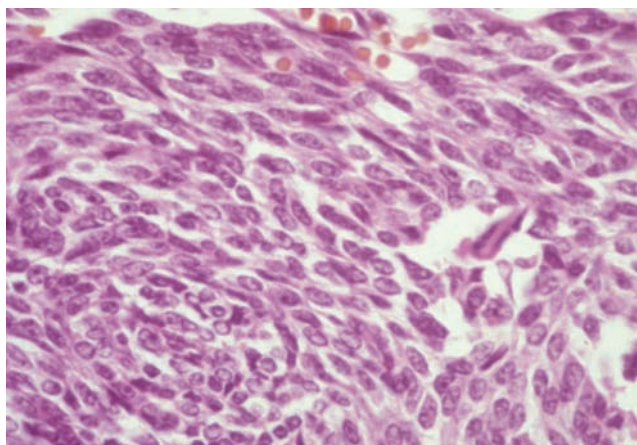


Figure 94. Typical carcinoid with focus of spindle cells. There is no nuclear molding or mitotic activity. Compare with Figure 99. (H&E, 400 $\times$).

gene product 9.5. They are also variably positive for a variety of peptides, including serotonin, calcitonin, bombesin, and somatostatin.

Electron Microscopy

TCs contain abundant membrane-bound, electron-dense neurosecretory granules varying in size from 90 to 230 nm (10). Cell junctional complexes are observed as well as numerous mitochondria if the TC is of the oncocyctic type.

Differential Diagnosis

See under "Atypical Carcinoid"

Treatment and Prognosis

Because radiation and chemotherapy are largely ineffective, surgery is the treatment of choice (15). The extent of resection should be as conservative as possible as long as complete removal is achieved. A neck dissection is not warranted.

In a review of 12 patients with TCs of the larynx, El-Naggar and Batsakis observed that 4 subsequently developed distant metastasis (liver, bones). At least one patient developed the carcinoid syndrome and another died of disease five years after treatment (4). Although this data suggest that TCs of the larynx are more aggressive than those of the lung, the sample size is very small and may not be statistically significant. It is also possible that some of these tumors on critical review utilizing current criteria might best be classified as atypical carcinoids.

C. Atypical Carcinoid

Clinical Features

The atypical carcinoid (AC) was first described in the larynx by Goldman et al. in 1969 (16). It is the most frequent neuroendocrine tumor of the larynx, being 5 to 15 times more common than the typical carcinoid (5,11).

At the time of diagnosis, patients with ACs have ranged from 20 to 83 years of age (average 61 years), and the majority (74%) have been men (5,17).

As with typical carcinoids, ACs arise primarily in the supraglottic larynx (96% of all cases), usually in the region of the aryepiglottic fold, arytenoid, or false vocal cord (5). They present as tan, gray, or hemorrhagic, 0.2- to 4.0-cm (average 1.6-cm) submucosal or polypoid growths, with or without surface ulceration (Fig. 95). Hoarseness and dysphagia are the usual presenting symptoms. Approximately one-fifth of patients also experience pain in the throat, and most have a history of smoking.

An associated paraneoplastic syndrome is exceptional (15,18). A rare case has also been associated with elevated levels of serum calcitonin (19,20).

The occurrence of multiple synchronous neuroendocrine tumors in the same patient is distinctly uncommon. Laccourreye et al. document such a case in a 48-year-old man who had an AC of the left false vocal cord—arytenoid cartilage area associated with a

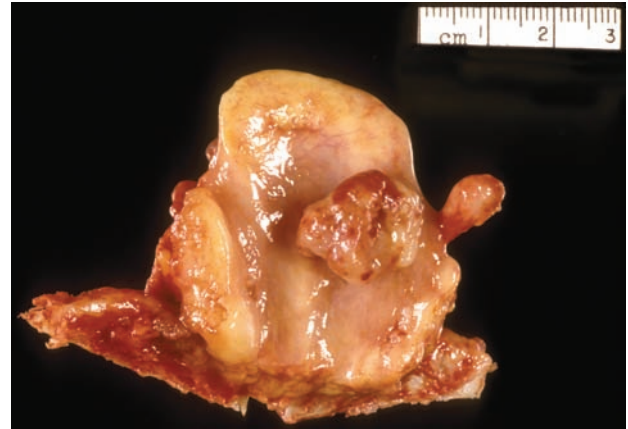


Figure 95. Polypoid atypical carcinoid arising from the epiglottis.

simultaneous neuroendocrine carcinoma of the pancreas (21).

Pathology

ACs are infiltrative tumors that grow in a variety of patterns, including small nests, sheets, cords or trabeculae, glands, rosettes, or a combination of these (Fig. 96). Cysts with intracystic papillary projections of tumor cells are also not uncommon. The ACs are distinguished from typical carcinomas by the presence of larger cells, prominence of nucleoli, occasional mitoses (up to 10/10 high power fields), necrosis, pleomorphism, and/or vascular and perineural invasion (Fig. 97).

Wenig et al. observed that 91% of their tumors displayed intracytoplasmic or intraluminal PAS-positive, diastase-resistant granules, and that 17% were mucicarmine-positive (22). Amyloid, although described, is uncommon in our experience.

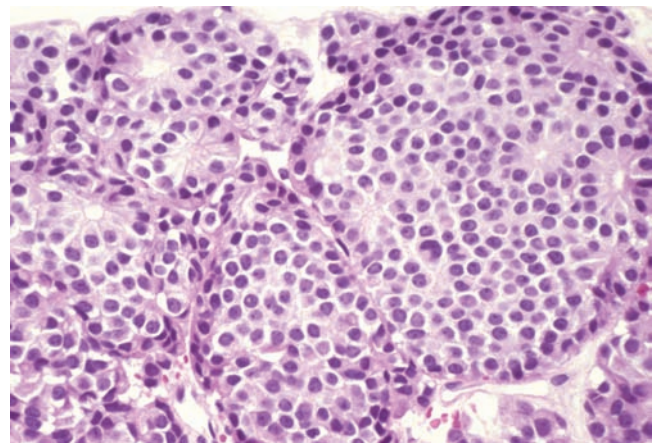


Figure 96. Atypical carcinoid composed of clusters of cells. Note the rosettes in the upper left hand corner (H&E, 200×).

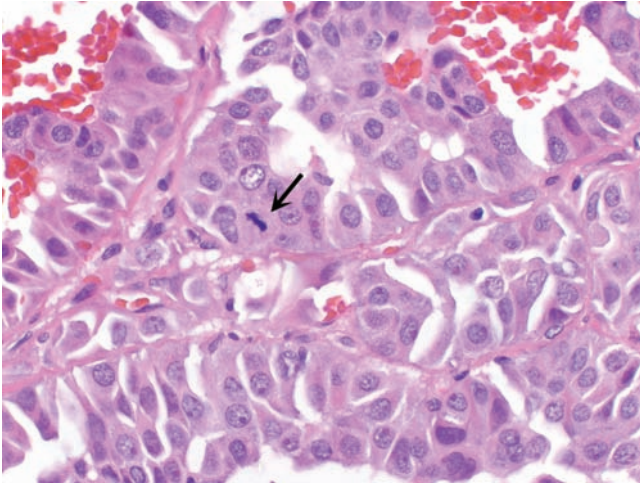


Figure 97. Atypical carcinoid. Note that the cells are larger than those seen in a typical carcinoid (compare with Fig. 93). Mitoses are frequent (arrow) and some cells contain nucleoli (H&E, 400 $\times$).

Immunohistochemistry

According to Woodruff and Senie, 100% of ACs are positive for synaptophysin, 96% for cytokeratin, 94% for chromogranin, 80% for calcitonin, 75% for carcinoembryonic antigen, and 21% for serotonin (5).

Electron Microscopy

Neurosecretory granules ranging from 70 to 420 nm are common, but they are less abundant than in typical carcinoids (10).

Differential Diagnosis

As previously indicated, ACs are distinguished from typical carcinoids by the presence of larger cells, prominence of nucleoli, occasional mitoses (up to 10 per 10 high power fields), necrosis, pleomorphism, and vascular and perineural invasion. Other tumors that are often confused with AC and the immunohistochemical stains that can be used to separate them are shown in Table 17. Two that deserve special attention are the laryngeal paraganglioma (LPG) and medullary

carcinoma of thyroid (MCT). For many years AC has been mistaken, especially on small biopsies, for LPG, which has accounted for the erroneous impression that up to 25% of all LPGs are malignant (7,10,23). The distinction is important for obvious reasons: ACs are often aggressive tumors, whereas LPGs are almost always benign. These two can easily be separated on the basis of any one of three immunostains: ACs are positive for keratin, carcinoembryonic antigen (CEA), and calcitonin, whereas LPGs are negative for these stains (see Table 17) (7,24).

In some instances, ACs may be difficult to separate from MCT, especially when dealing with metastatic lesions (19,23,25,26). This is not unexpected because both tumors are usually positive on immunostaining for synaptophysin, calcitonin, CEA, and occasionally, even for serotonin. Clinical and radiologic studies to detect the presence or absence of a mass in the larynx or thyroid can be very helpful in resolving this dilemma. Although the serum calcitonin level is almost invariably elevated in metastatic MCT and usually negative in AC, Sweeney et al. and Smets et al. have reported two cases of laryngeal AC associated with elevated levels of serum calcitonin (19,20). Reliance on this test to distinguish between these two tumors is, therefore, not absolute. Knowledge of the serum CEA, however, may be helpful. This test is almost universally elevated in metastatic MCT, but thus far, has not been reported in association with AC (24,25). Staining for amyloid may offer some supportive evidence for MCT. Although amyloid has been described in AC, it is uncommon in our experience, but found in 75% to 80% of MCT. It has been suggested that thyroid transcription factor (TTF) may be used to separate the AC from MCT, it being diffusely and strongly positive in medullary carcinoma and negative or, at most, only focally weakly positive in AC. Subsequent experience, however, has shown significant variation in the expression of TTF in AC and, accordingly, TTF may not be as important a discriminator as initially thought.

Treatment and Prognosis

In a review of 127 ACs of the larynx, Woodruff and Senie found metastases to cervical lymph nodes in 43%, to skin and subcutaneous tissue in 22%, and to

Table 17 Differential Diagnosis of Laryngeal Tumors^a

Stain	Carcinoid tumor ^b	Paraganglioma	Medullary carcinoma of thyroid	Hemangiopericytoma	Melanoma	Renal cell carcinoma
Keratin	+	—	+	—	—	+
CEA	+	—	+	—	—	—
Synaptophysin	+	+	+	—	—	—
Calcitonin	+/-	—	+	—	—	—
Thyroid transcription factor	+/-	—	+	—	—	—
Tyrosinase	—	—	—	—	+	—
Renal cell carcinoma antigen	—	—	—	—	—	+
Congo red	— ^c	—	+	—	—	—

^aTypical staining pattern; variations may occur.

^bIncludes typical and atypical carcinoids.

^cAlthough amyloid may be found in carcinoids, most are negative.

other distant sites in 44% (particularly lungs, liver, and bones) (5). The 5- and 10-year cumulative survival rates were, respectively, 48% and 33%. Survival was particularly worse among patients who developed cutaneous-subcutaneous metastases. Because most ACs of the larynx are aneuploid, determination of DNA ploidy does not offer any additional prognostic information (29).

Similar to typical carcinoids, ACs are also relatively resistant to irradiation and chemotherapy (15). Surgery, therefore, is the mainstay of treatment. The extent of surgical excision depends on the size and location of the tumor, but usually requires a partial or total laryngectomy. Because of the high incidence of cervical lymph node involvement, a neck dissection, even when the lymph nodes are clinically negative, is warranted.

D. Small Cell Neuroendocrine Carcinoma

Clinical Features

Small cell neuroendocrine carcinoma (SCNEC) of the larynx was first described by Olofsson and van Nstrand in 1971 (30). Although it is the second most common neuroendocrine tumor of the larynx, it is still an infrequent neoplasm representing only 0.5% of all laryngeal carcinomas (6).

SCNEC of the lung, on the other hand, is a common tumor. Because the larynx is, in part, embryologically related to the lungs, it is not surprising that the tumor could also arise *de novo* in the larynx. The apparent rarity of SCNEC in this site and the length of time it has taken to recognize it as such is remarkable. In all likelihood, the tumor has gone unrecognized and probably has been mislabeled as a poorly differentiated squamous cell carcinoma or as an anaplastic carcinoma.

In the larynx, the tumor is more common in men by a ratio of 3:1, with an age range of 23 to 91 years (6). Only 3% occur in patients younger than 40 years of age. Hoarseness and dysphagia, often associated with painless cervical lymph node metastases, are the most common symptoms. Most are heavy smokers.

Pathology

Although SCNEC can occur anywhere in the larynx, the majority are of supraglottic origin. The tumors are often ulcerated and, as a consequence, there are no gross characteristics that distinguish it from ordinary squamous cell carcinoma (Fig. 98).

In the past, SCNECs were often divided microscopically into three types—oat cell (composed of spindle cells), intermediate (composed of round cells) and combined (composed of both spindle and round cells). This classification has no prognostic significance and is now largely abandoned.

The tumor grows in the submucosa as sheets or ribbons of closely packed cells, with indistinct cytoplasm and round, oval, or spindled, hyperchromatic nuclei without nucleoli (Fig. 99). Mitoses, necrosis, and lymphatic, vascular, and perineural invasion are

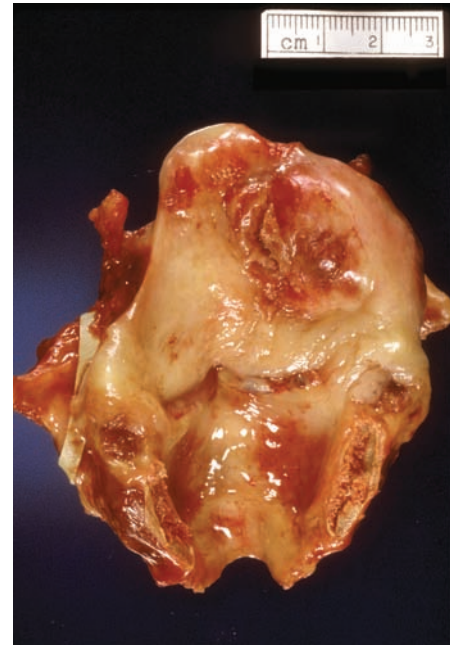


Figure 98. Ulcerated small cell neuroendocrine carcinoma.

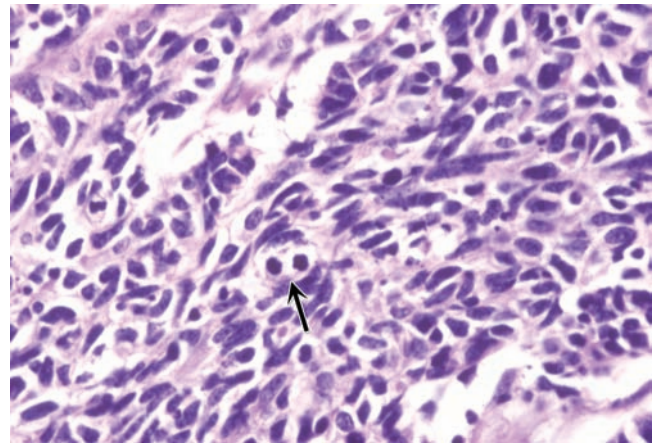


Figure 99. Small cell neuroendocrine carcinoma composed of cells with poorly defined cytoplasm and spindled hyperchromatic nuclei. Note the nuclear molding and mitoses (arrow). Compare with Fig. 94.

common, as well as nuclear molding and DNA coating ("hematoxyphilia") of the walls of blood vessels. Rare rosette formation may also be seen. The mucosa is often ulcerated, but the marginal epithelium is free of significant dysplasia or *in situ* carcinoma.

In a few instances, SCNEC may also contain foci of squamous cell carcinoma, adenosquamous, or even rhabdomyosarcoma (see "combined SCNEC" below) (2,31).

Immunohistochemistry

SCNEC is usually positive for AE1/3, synaptophysin, CD56, and TTF and negative for p63.

Electron Microscopy

Membrane-bound, electron-dense neurosecretory granules ranging from 50 to 200 nm are scant compared with the typical and atypical carcinoid (10).

Differential Diagnosis

The differential diagnosis includes TC, AC, BSCC, malignant lymphoma, and a metastasis from a primary SCNEC of the lungs. Compared with TC and AC, SCNEC is composed primarily of short spindle cells without nucleoli and exhibits more nuclear molding, necrosis, and mitoses. In addition, SCNEC is variably positive for TTF and negative for CEA and calcitonin while the AC is positive for CEA and calcitonin and variably positive for TTF (28).

BSCC is a biphasic tumor composed of basaloid and squamous cell components that characteristically grow in a lobular pattern with central comedonecrosis. In addition BSCC often exhibits prominent vesicular to hyperchromatic nuclei, nucleoli, cyst-like areas and hyalinosis (Table 15). BSCC is also negative for neuroendocrine markers and TTF. Malignant lymphomas are positive for leukocytic common antigen and negative for neuroendocrine markers. A metastasis from a primary SCNEC of the lung is based on negative imaging studies of the lung.

Treatment and Prognosis

The clinical course of SCNEC of the larynx is aggressive, with early regional and distant metastases. Almost half of patients present with positive cervical lymph nodes and about 60% to 90% will develop distant dissemination, especially to the lungs, liver, and bones (30,33). In contrast to SCNEC of the lung, only 8% of SCNECs of the larynx metastasize to the central nervous system and then only as a preterminal event (33). The two- and five-year survival rates are, respectively, 16 and 5% (6).

Because most patients have disseminated disease at diagnosis, radical surgery (laryngectomy with neck dissection) is rarely indicated. Instead, a therapeutic protocol using a combination of local irradiation and chemotherapy, similar to that in pulmonary SCNEC, is advocated (15). Because of early intralesional angiolymphatic invasion, survival does not necessarily correlate with the size of the tumor.

A few laryngeal SCNECs have been associated with hormonally active paraneoplastic syndromes. Among these are included the Schwartz-Bartter syndrome (hypersecretion of antidiuretic hormone), Eaton-Lambert syndrome (myasthenia gravis-like syndrome), and Cushing's syndrome (ACTH production) (18,34–37).

E. Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinomas (LCNEC) of the larynx, similar to those described in the lung, are rare

and have usually been included under the category of ACs (1,2,38–40). Microscopically these tumors are characterized by large cells (generally 3 times the size of the nucleus of a resting lymphocyte) with moderate amounts of cytoplasm, prominent nucleoli, more than 10 mitoses per 10 high power fields, frequent necrosis, and positive staining with neuroendocrine markers.

To date, no large series of LCNECs of the larynx, as defined above, have been described and therefore the clinicopathologic features and prognosis in this site are unknown. Although in the lung it has been stated that there is no difference in prognosis between SCNECs and LCNECs when stratified by stage, the overall five-year survival rates for LCNECs has ranged from 13% to 47% (1,41). Therapy for LCNEC is not standardized and has varied from the use of protocols used to treat SCNEC to surgical excision (42).

F. Combined Small Cell Neuroendocrine Carcinoma

SCNEC associated with a squamous or adenocarcinomatous component are referred to as combined or composite carcinomas. They are unusual representing less than 10% of all SCNECs of the larynx. Only 14 cases have been described as of 2004 (43). Most, if not all, were associated with a squamous cell carcinoma, either in situ or invasive. The patients were all men with an age range of 41 to 83 years (median 55 years), and all had a significant smoking history. The overwhelming majority had supraglottic tumors and none was associated with a paraneoplastic syndrome. The tumors are aggressive with a behavior similar to “pure” SCNEC and death from disease usually within two years of diagnosis (43).

G. Paraganglioma

Paragangliomas of the larynx are discussed in chapter 12.

XXIV. SALIVARY GLAND-TYPE NEOPLASMS OF THE LARYNX**A. Introduction**

Although mucoserous glands are sparse to absent in the glottis, they are rather prominent in the supraglottis and subglottis. Yet, paradoxically, salivary-type neoplasms are uncommon, constituting no more than 1% of all laryngeal neoplasms (1,2). Because of their rarity, no single institution has accumulated a large series; therefore, details of their clinical and pathological behavior come only through composite analysis of single case reports or small series. Alleged cases contained in the older literature are particularly frustrating; they are often poorly documented and do not conform to modern-day classification.

Although these tumors can occur in all ages, most present in the 50- to 70-year age group and about 60% to 80% of the patients are men. Most of the neoplasms are malignant and, among these,

adenoid cystic carcinoma and mucoepidermoid carcinoma are the most frequent types. Because these tumors are rare, the differential diagnosis must always include the possibility of a metastasis from a distant site. The location, symptomatology, and behavior of these neoplasms are correlated, to some extent, with the specific histological type and, therefore, they will be considered separately. See chapter 10, "Diseases of the Salivary Glands" for gross and histologic description of each of the following tumors.

B. Pleomorphic Adenoma

Although pleomorphic adenoma is the most frequent tumor of the major salivary glands, it is unusual in the larynx. Of 391 pleomorphic adenomas tabulated at the University of Pittsburgh through 1976, only one (0.25%) occurred in the larynx (3).

In 1997, Dubey et al. reported a pleomorphic adenoma and identified 20 additional cases in a review of the world literature (4). These occurred in 12 males and 9 females, ranging in age from 15 to 82 years (average 51 years). The tumors were generally well demarcated and varied in size from 1 to 6 cm. Fourteen arose in the supraglottic larynx (usually the epiglottis), three in the glottis and four in the subglottis. Most were treated by surgery and at the last follow-up, none was known to recur.

Pleomorphic adenomas may contain areas of squamous epithelium, which may represent a potential pitfall. MacMillan and Fechner, for instance, have reported a pleomorphic adenoma of the larynx that had ulcerated and undergone peripheral squamous metaplasia. A biopsy from this area was subsequently misinterpreted as a squamous carcinoma and the patient underwent unnecessary irradiation (5).

A few cases of carcinoma ex pleomorphic adenoma of the larynx have been reported (6–8). Some of these, especially the case of Sabri and Hajjar are questionable (6).

C. Oncocytic Lesions

Virtually all oncocytic lesions of the larynx are examples of what have been referred to as oncocytic cysts or oncocytic papillary cystadenomas. Whether they are true neoplasms or a cystic metaplastic-hyperplastic response to various stimuli is the subject of ongoing debate.

Such lesions, hereafter referred to as oncocytic papillary cystadenomas (OPC), arise from the ducts of laryngeal mucoserous glands and, as such, occur primarily in region of the false vocal cords and ventricles. They affect both sexes about equally and are uncommon in individuals younger than 50 years of age. Of 35 cases on file at the University of Pittsburgh, the average age is 69 years (range 55–82) (9).

Hoarseness is, by far, the most frequent complaint. Dyspnea, stridor, pain, foreign body sensation, and dysphagia have also been reported.

When viewed endoscopically, OPCs appear as smooth, cystic, submucosal masses that rarely exceed

1 or 2 cm (Fig. 14). Histologically, the cysts often contain intraluminal papillary projections (Fig. 18). The cysts as well as the papillae are lined or covered by multiple layers of large, uniform, deeply eosinophilic columnar cells that, by electron microscopy, contain numerous mitochondria. The nuclei are small and dark and situated near the center of the cells. The contents of the cysts vary from watery to mucoid.

The treatment of choice depends on the extent and location of the lesion, but usually entails microlaryngoscopy and excision. Inadequate removal may result in recurrence. Because some OPCs may be multicentric, it is important for the surgeon to thoroughly examine the laryngeal mucosa to determine the extent of the disease. The OPCs have no malignant potential; however, a few have been found incidentally in association with squamous cell carcinoma of the larynx (10).

D. Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) of the larynx is a distinctly uncommon tumor (11–19). In a review of 264 ACC from all sites in the head and neck on file at the Memorial Hospital in New York, Spiro et al. identified only three (1.1%) that originated in the larynx (20). As of 1993, only about 120 cases have been reported in the larynx in a review of the world literature (21).

The tumor affects both sexes about equally and occurs over a broad age range, with a peak incidence between 50 and 70 years. Approximately 50% to 60% arise in the subglottic and 25% to 35% in the supraglottic larynx (11,14) (Figs. 100–102). Only 5% to 10% involve the glottis. Airway obstruction, dysphagia,

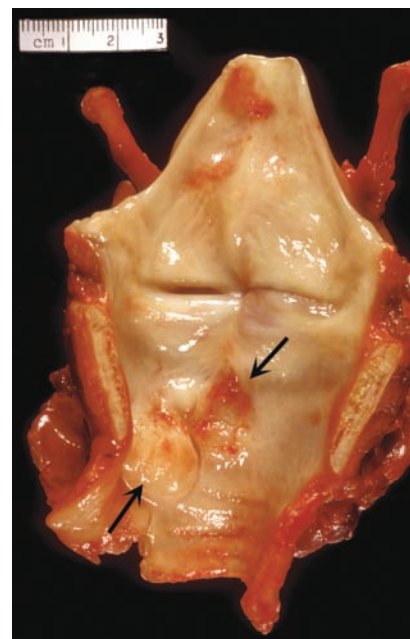


Figure 100. Adenoid cystic carcinoma of subglottic larynx (arrows).



Figure 101. Adenoid cystic carcinoma. Cross section of tumor shown in Figure 100. The tumor has invaded into the adjacent soft tissue.

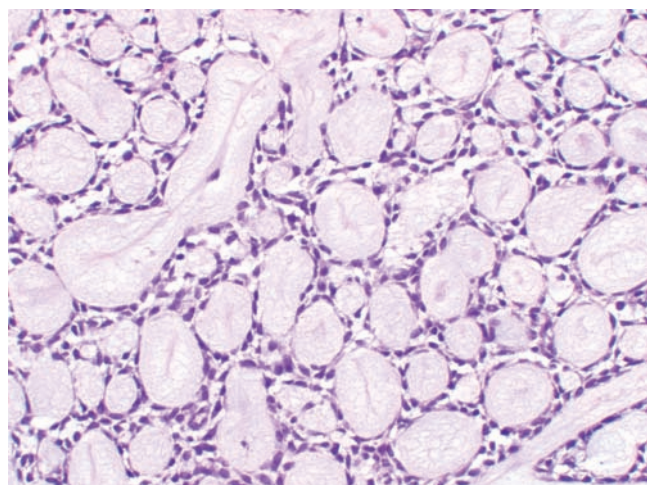


Figure 102. Microscopic view of adenoid cystic carcinoma shown in Figures 100 and 101 (H&E, 100 $\times$).

hoarseness, cough, sore throat, and occasionally, pain are the usual presenting symptoms.

Although some studies have indicated a rather significant incidence of cervical lymph node metastases, especially for those arising in the supraglottic larynx, we suspect that in most of these cases the lymph nodes were involved by direct tumor extension or that the tumor was some other neoplasm incorrectly labeled as an ACC. In our experience, embolic nodal metastasis by ACC is infrequent.

Two recently recognized tumors of the larynx that may be confused with ACC are the BSCC and carcinoid tumor (typical and atypical). In contrast with ACC, BSCC often exhibits pleomorphism, necrosis, and frequent mitoses and, in addition, contains either in situ or invasive component of squamous cell

carcinoma (Table 14). A carcinoid can be excluded on the basis of its immunopositivity for neuroendocrine markers, such as synaptophysin.

Surgery is the treatment of choice for ACC of the larynx, with the extent of the procedure being dependent on tumor site. Because most are of subglottic origin, a total laryngectomy is usually required, whereas partial procedures may be sufficient for those involving the supraglottic larynx. A neck dissection is not warranted unless the nodes are enlarged or have been shown to contain tumor. Radiation therapy may produce temporary regression, but rarely permanent control.

Because of their rarity and lack of significant follow-up, the long-term prognosis is largely unknown. A few patients, however, have been reported to be alive and disease-free as long as 15 years or more (16). The absence of lymph node metastasis cannot be considered a favorable prognostic sign, for most ACC metastasize systematically through the blood stream, usually to lung, bone, or liver. Patients may, however, live several years after developing metastases.

E. Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) and adenosquamous carcinoma are often erroneously assumed to be synonyms. The former, however, is a type of salivary-mucoserous carcinoma while the latter is a variant of squamous cell carcinoma. These limitations, must be considered when viewing reports of MECs in uncommon sites, such as the larynx (22).

According to Prgomet, 80 cases of MECs of the larynx have been reported as of 2003, of which some degree of information was available on 63 (23). Of these, 70% occurred in males and 30% in females with an average age of 57 years. Fifty-seven percent were of supraglottic origin, 30% glottic, 8% subglottic, and 5% transglottic. At least 30% developed metastases, primarily to cervical lymph nodes.

It is not uncommon in small biopsies for MEC to be mistaken for squamous cell carcinoma. Because MECs are only moderately responsive to radiotherapy, surgery offers the best opportunity for cure. The histological grade as well as anatomical site of the tumor influence the extent of the surgical procedure. Patients with high-grade supraglottic tumors (and possibly intermediate-grade tumors) may be treated by supraglottic laryngectomy and neck dissection, even if the lymph nodes are clinically negative. A neck dissection is not warranted for low-grade tumors.

The overall five-year survival rate for all grades of laryngeal MEC is 75% to 80% (22). For low-grade tumors, the five-year survival is 90% to 100% and, for high-grade tumors, 50% to 55% (22). Distant metastases have occurred in about 10% of cases, primarily to lung, brain, bone, and kidney.

F. Other Tumors

A limited number of other salivary-type neoplasms have also been described in the larynx. Because of their scarcity, no generalizations concerning prognosis

can be made. Among these are included acinic cell carcinoma (24), clear cell carcinoma (25,26), benign and malignant myoepitheliomas (27,28), epithelial-myoepithelial carcinoma (29), salivary duct carcinoma (30,31), oncocytoma and oncocytoid adenocarcinoma (32,33), papillary adenocarcinoma (34) and mucoid adenocarcinoma (35).

XXV. MELANOTIC LESIONS OF THE LARYNX

A. Melanosis

"Melanosis" is a clinical term, much like leukoplakia, which can be loosely applied to any melanin-containing lesion, be it congenital or acquired, benign or malignant, or simply the result of physiological stimulation. In the case of mucous membranes, it is most often used to describe a flat or slightly elevated solitary or multifocal area of benign melanin pigmentation with associated melanocytes, the border of which varies from well to poorly defined (1).

Melanosis has been observed in both white and black populations. It is relatively common in the oral cavity, less frequent in the nasal cavity, and rare in the larynx. The melanocytes and pigment are usually confined to the basal layer of the mucosa, but on occasion, can be found in the stroma or in the walls of mucoserous glands (Fig. 103). Their presence in the endodermally derived larynx is probably best explained by erratic migration of melanocytic precursors from the neural crest during embryogenesis (2). Other theories have postulated a metaplasia of squamous or glandular epithelium into melanocytes, or the transformation of various neural elements into melanocytes (2).

With the exception of the oral cavity, these cells, when present, rarely produce enough pigment to be grossly detectable unless stimulated by local irritation, inflammation, or radiotherapy; the latter is analogous to the effect of sunlight on epidermal melanogenesis

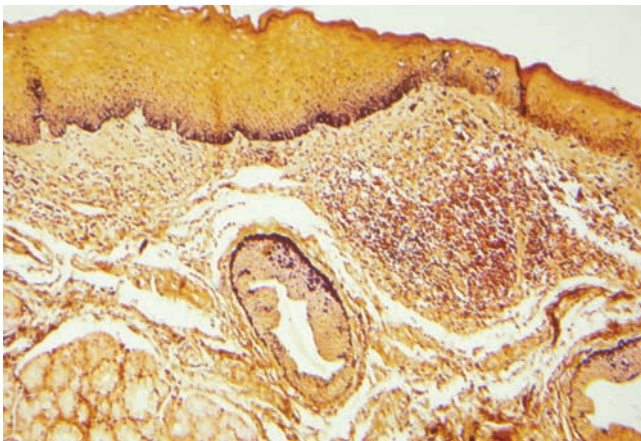


Figure 103. Melanosis of the epiglottis. Note the melanin (dark-staining areas) in the basal region of the squamous mucosa and in the duct of a mucoserous gland (Warthin-Starry melanin, 40 $\times$).

(3). The significance of melanocytes in the larynx is that they may rarely give rise to nevi and malignant melanoma.

In 1997, Gonzalez-Vela et al. reported four cases of melanosis of the larynx and found only 13 additional cases in an extensive review of the literature (4). These 17 patients were aged between 53 and 86 years (median 59 years), and of the 16 in which the gender was known 15 were males and one female. Nine cases involved the true vocal cords, five the supraglottic larynx, two the false vocal cords, and in one, the site was unknown. At least half, and maybe more, of the cases occurred in individuals with a history of smoking. Only 25% of the cases, however, were associated with gross pigmentation.

Nine of the 17 cases of melanosis were associated with laryngeal neoplasms—seven squamous cell carcinomas and two malignant melanomas (4).

Whether melanosis might be related to malignant melanomas is unknown. In a review of 22 malignant melanomas of the larynx only 2 (9%) were associated with melanosis (5). None of the four laryngeal melanomas reported by Wenig showed this associated (6). The link, therefore, between mucosal malignant melanomas and melanosis is apparently weak. Likewise, since squamous cell carcinoma and possibly even melanosis are related to smoking, the two events occurring concurrently is most likely a coincidental finding. Nevertheless, the presence of melanosis in the larynx may warrant the need for thorough evaluation and surveillance to exclude carcinoma or melanoma.

B. Nevus

Nevi of the larynx are extremely rare, with only a handful of cases contained in the world literature. Seals et al. describe a junctional nevus of the left true vocal cord in a 10-year-old black girl and Schimpf et al. report a compound nevus of the plica ventricularis (false vocal cord) (7,8). Wenig also illustrates what appears to be a compound nevus of the larynx, but provides no additional information (9). Travis et al. report a 65-year-old black man who had a malignant melanoma of the oral cavity associated with an alleged lentigo of the right pyriform sinus (10). A photomicrograph of the "lentigo," however, is more consistent with melanosis, as described above, rather than a lentigo.

Nevi of the larynx, especially in older patients, should be excised to rule out malignant melanoma. Whether they have any malignant potential is unknown.

C. Malignant Melanoma

Clinical Features

Primary malignant melanoma of the larynx (PMML) is an exceptionally rare neoplasm, with only 22 cases recorded in the world literature in 1986 and 54 cases in 2001 (5,6,11). The Otolaryngic Tumor Registry at the Armed Forces Institute of Pathology contains only nine cases (0.09%) among 10,270 primary laryngeal neoplasms accumulated over a 75-year interval (9).

The tumor is more common in men (85% of all cases) and has been described in individuals from 35 to 86 years of age (average about 58 years) (5,6). Almost all of the tumors reported thus far have occurred in whites.

Most (60–80% of all cases) arise in the supraglottic larynx and present as an exophytic polypoid or sessile, occasionally ulcerated, black, brown, gray, pink, or white mass, ranging anywhere from 3 mm to 8.0 cm (5,9). A few have been associated with laryngeal melanosis (4,5).

Dysphagia, sore throat, hoarseness, pain, intermittent hemoptysis, and a cervical (metastatic) mass are the usual presenting manifestations. Although most tumors have occurred in individuals who are smokers and consumers of alcohol, it remains uncertain whether these factors are etiologically significant.

Pathology

Similar to melanomas elsewhere, PMMLs are composed predominantly of epithelioid or spindle cells that grow, respectively, in an alveolar or fascicular-storiform pattern. The cells typically have eosinophilic cytoplasm and nuclei that range from vesicular to hyperchromatic, with or without prominent nucleoli. Nuclear pleomorphism, multinucleated tumor giant cells, intranuclear inclusions of cytoplasm, mitoses, and necrosis are not uncommon. Because of surface ulceration, junctional activity may or may not be seen.

About one-third of PMML are amelanotic, requiring a high index of suspicion when dealing with this tumor. Special stains for melanin, such as the Warthin-Starry stain, and immunohistochemical procedures for S100 protein, HMB-45 and tyrosinase, are important in confirming the diagnosis. In instances for which these procedures are negative or equivocal, electron microscopy for the presence of premelanosomes and melanosomes is helpful.

Differential Diagnosis

Before the diagnosis of PMML can be accepted, metastatic malignant melanoma (MMM) from another site must be excluded. MMM is considerably more common than PMML and accounts for 30% to 40% of all metastatic tumors of the larynx (12–16). In general, PMML presents as an exophytic mucosal lesion, often associated with junctional activity and positive cervical lymph nodes. MMM of the larynx, on the other hand, is usually submucosal and not associated with junctional activity or enlarged cervical lymph nodes. Furthermore, MMM of the larynx is usually a preterminal event, associated with a known primary and multiorgan dissemination. It should be emphasized again that because of surface ulceration, junctional activity may not always be apparent in PMML. Wenig also indicates that since melanocytes can be identified in mucoserous glands or stroma that it is possible that a PMML may take origin from these melanocytes and not arise from the surface epithelium. Hence, the presence of an in situ or junctional component is not always required to postulate a primary origin in the larynx (6).

Amelanotic PMMLs that grow in a spindle or storiform pattern must also be distinguished from monophasic spindle cell squamous carcinoma and malignant fibrous histiocytoma. This can usually be accomplished by the use of immunostains for cytokeratin, S-100 protein, and HMB-45. PMML is negative for cytokeratin and positive for S-100 protein and HMB-45. All three of these stains are negative in malignant fibrous histiocytoma.

Other tumors, particularly typical and atypical carcinoids, paraganglioma, and renal cell carcinoma, may also enter into the differential diagnosis. Stains that are helpful in distinguishing these neoplasms are shown in Table 17.

Treatment and Prognosis

Primary malignant melanoma of the larynx is associated with a poor prognosis, with an average survival of about three years (5). Although PMMLs exhibit a lower incidence of local recurrence compared with other mucosal melanomas of the head and neck, about 80% are associated with positive cervical lymph nodes sometime during the course of the disease, and 80% will eventually develop distant metastases (5).

Complete surgical resection is the treatment of choice. Depending on the site of origin and stage of disease, this will usually involve a partial or total laryngectomy and probable cervical lymph node dissection.

XXVI. GIANT CELL TUMOR

A. Introduction

The giant cell tumor of the larynx is identical to the giant cell tumor seen elsewhere in the skeleton and, as such, is defined as a benign but locally destructive neoplasm composed of sheets of ovoid to spindle-shaped mononuclear cells with uniformly dispersed osteoclast-like giant cells (1–6).

They are very rare in the larynx, representing only 0.09% of 8995 benign and malignant primary laryngeal neoplasms accessioned at the Armed Forces Institute of Pathology during the years 1966–2000 (1).

B. Clinical Features

Of 28 reported cases, 25 were in men and 3 in women, aged 23 to 62 years (mean about 40–45 years) (1). Most originate from the thyroid cartilage, followed by the cricoid cartilage and epiglottis. The tumors enlarge slowly and manifest as palpable neck masses, hoarseness, airway compromise, dysphagia, or sore throat.

On imaging, it often appears as a tumor exploding from within the cartilage, destroying it, and extending into the soft tissue of the neck or endolarynx.

C. Pathology

Most tumors have ranged from 2.4 to 7 cm (mean about 4–4.5 cm) and have been centered in the thyroid or cricoid cartilages, especially in the normally

ossified portions of these cartilages (1). On cut section, they are soft, red to grey-pink and frequently extend beyond the cartilage into the adjacent soft tissue. Hemorrhage and cystic degeneration are common.

The tumors are similar histologically to giant cell tumor of bone and, as such, consist of a dual population of cells: mononuclear cells and osteoclast-like giant cells. The mononuclear cells appear as broad sheets of cells reminiscent of histiocytes. They are round, ovoid or spindle and have pink to amphophilic cytoplasm and round, vesicular nuclei with occasional prominent nucleoli. The giant cells are evenly distributed throughout the tumor and contain up to 20 or more nuclei per cell. The nuclei of the giant cells are identical to those of the mononuclear cells.

The stroma is vascular and contains many thin-walled vessels with small areas of hemorrhage and hemosiderin-laden macrophages. Mitoses are usually seen, averaging 4 per 10 high power fields (range 1–12 per 10 high power fields) (1). Atypical mitoses are not seen.

D. Differential Diagnosis

This includes giant cell (reparative) granuloma, brown tumor of hyperparathyroidism, fibrous histiocytoma, and a pleomorphic carcinoma. Giant cell granuloma of the cricoid cartilage is exceptionally rare (7). The giant cells in this tumor are not evenly distributed, but rather concentrate around areas of recent and/or old hemorrhage. A giant cell granuloma also exhibits more stromal fibrosis. A brown tumor is identical histologically to the giant cell granuloma, but is associated with an elevated serum calcium. A benign fibrous histiocytoma contains a more uniform storiform arrangement of fibroblasts and does not show a symmetrical distribution of giant cells. A malignant fibrous histiocytoma (giant cell type) exhibits significant nuclear pleomorphism and abnormal mitoses, none of which are seen in giant cell tumor. A pleomorphic carcinoma will not only show abnormal mitoses and pleomorphism, but will also be positive for cytokeratin.

E. Treatment and Prognosis

Complete, but conservative surgical excision is the treatment of choice. Large tumors may require a partial or total laryngectomy. Adjuvant therapy is unnecessary.

There have been no convincing records of local recurrence or malignant behavior secondary to giant cell tumor of the laryngeal framework.

XXVII. INFLAMMATORY MYOFIBROBLASTIC TUMOR

A. Introduction

Inflammatory myofibroblastic tumor (IMT), also known as inflammatory pseudotumor and plasma cell granuloma, is an enigmatic lesion composed of myofibroblastic spindle cells with an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils (1). It may occur in any anatomic site, especially the lungs.

B. Etiology

Traditionally, it has been regarded as a nonneoplastic condition, possibly related to trauma or an infectious-immunologic process, which generally responds to systemic corticosteroids, conservative excision, or even radiotherapy. The recent finding of human Herpes virus-8 DNA sequences and overexpression of interleukin-6 and cyclin D1 in some IMTs does add credence to an infectious etiology (2). Those alleged cases involving lymph nodes, liver and spleen associated with the EBV are, however, probably unrecognized follicular dendritic cell tumors (3).

Not all IMTs, however, exhibit a bland behavior. Some are locally destructive, especially in the sinonasal tract, while others have recurred following excision, and a few allegedly have even metastasized, behaving in this regard, more like a true neoplasm. The observation that some lesions are aneuploid or clonal on cytogenetic evaluation supports this contention, and raises the issue of whether some IMTs should be considered as a borderline or low-grade malignant tumor, especially those composed predominantly of myofibroblasts (4–8). From the above observations, it would appear that IMTs may represent a diverse group of lesions of multiple etiologies that only share a common histologic bond—a tumoral mass of inflammatory cells with a variable myofibroblastic-fibrous tissue response.

C. Clinical Features

IMT has been described in a variety of sites in the head and neck, including the orbit, sinonasal tract, middle ear-mastoid, oral cavity, larynx, neck, and major salivary glands (9–16).

The larynx, which is the focus of the remaining discussion, is an uncommon site (3,17–22). In a review of 14 cases of IMTs in the larynx, 10 recurred in males and four in females aged 2 to 74 years (average 46 years) (17–21). Ten tumors arose from the true vocal cords, two were of supraglottic and two subglottic origin. Most presented with hoarseness or, infrequently, with a sensation of a foreign body in the throat or as airway compromise.

Some IMTs (15–30%) may also be associated with constitutional symptoms (fever, impaired growth, weight loss, malaise) or laboratory abnormalities (anemia, thrombocytosis, leukocytosis, polyclonal hyperglobulinemia, elevated erythrocyte sedimentation rate). Production of cytokines, especially interleukin-6, are thought to be responsible for the systemic effects. Most of the IMTs associated with systemic symptoms are found in the abdominal cavity. Guilemany et al., however have reported such a tumor in the larynx (21). The patient, a 62-year-old man, had a 3 cm IMT of the right true vocal cord associated with a 20 kg weight loss, fever, and an elevated erythrocyte sedimentation rate over a six-month period. Following excision, the patient regained his normal body weight with disappearance of his fever and normalization of the erythrocyte sedimentation rate four months later.

D. Pathology

IMTs are typically smooth, polypoid or nodular with a fleshy to firm consistency. They have ranged in size from 0.4 to 3.5 cm (13,21).

Histologically, they consist, in varying proportions, of inflammatory and spindle-fibrous components. The inflammatory element is typically polymorphous and composed of lymphocytes, plasma cells, histiocytes, eosinophils and, infrequently, neutrophils. The lymphocytes are mature, and, on immunostaining, are composed of both T and B cells. They may be randomly distributed or aggregate in small nodules with or without germinal centers. The plasma cells are also mature and polyclonal. Large sheets of plasma cells are unusual. Eosinophils vary from rare to numerous, and neutrophils, if seen at all, are usually near areas of necrosis or surface ulceration. The histiocytes are bland and may process small, barely visible nucleoli.

The fibrous component consists of cytologically bland spindle to stellate cells with characteristics of fibroblasts and/or myofibroblasts. The nuclei vary from round to elongated and vesicular to mildly hyperchromatic with moderate amounts of basophilic to eosinophilic cytoplasm.

Some lesions contain very little stroma while others are composed almost entirely of densely, sclerotic, hypocellular collagen with a laminated or keloidal appearance. Mitoses are infrequent and necrosis, if seen at all, tends to be spotty, unless the lesion has ulcerated the mucosal surface.

The fibroinflammatory process may encase nerves and blood vessels, forming concentric rings of collagen ("onion skinning") around them. Although blood vessels may show obliterative changes, inflammatory cells in the walls of blood vessels are rare to absent.

On the basis of the proportion of inflammatory and fibrous components, four histologic patterns are recognized: (i) *myxoid-granulation tissue* which contains plump spindle to stellate cells lying in an edematous, highly vascular, inflammatory background, (ii) *compact* comprised of a more prominent element of closely approximated spindle cells with admixed inflammatory cells, (iii) *sclerotic* made up of dense, eosinophilic, relatively acellular collagen with scattered inflammatory cells, and (iv) *mixed* composed of two or more of the preceding patterns (Fig. 104).

According to Hussong et al., IMTs that contain ganglion-like cells and exhibit cellular atypia, atypical mitoses, p53 expression, and DNA aneuploidy are aggressive and might warrant the diagnosis of a malignant IMT (6).

E. Immunohistochemistry

Data collected from several series (including all sites, not just the larynx) indicate that almost all IMTs are positive for vimentin, 87% for muscle specific actin, and 82% for smooth muscle actin (22). About half are focally or diffusely positive for desmin and about a third may focally express cytokeratin (22). Cook et al.

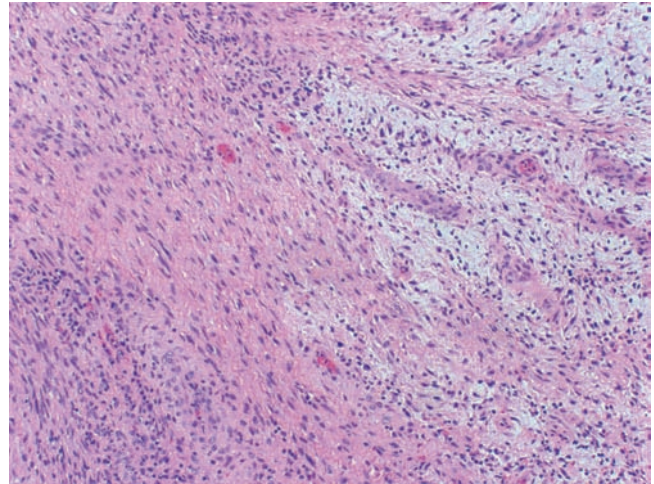


Figure 104. Inflammatory myofibroblastic tumor composed of both compact and myxoid areas with admixed inflammatory cells (H&E, 100×).

observed that 60% of the cases were positive for anaplastic lymphoma kinase (ALK) especially in younger patients (7). Those tumors occurring in patients over 40 years of age are usually ALK-negative.

F. Differential Diagnosis

The differential diagnosis can be exhaustive and has been covered in detail by others (23). In the larynx, SPCC (spindle cell carcinoma) should be excluded. This may be difficult, if not impossible, on small biopsies coupled with the fact that some IMTs are also focally positive for cytokeratin. In this instance, look for cells with atypical mitoses and dyskeratosis as well as mucosal changes of dysplasia or CIS. These findings should suggest SPCC. In addition, unless ulcerated, SPCC usually does not have a large component of inflammatory cells. SPCC is also often positive for p63 while the IMT is negative.

G. Treatment and Prognosis

Treatment has ranged from corticosteroids, conservative excision, laser therapy, and irradiation with varying degrees of success. Of 14 cases involving the larynx, at least three (21%) recurred following initial therapy (13,19,21). This compares with a recurrence rate of 25% for all other IMTs. In one case, the tumor recurred twice over a two-year period and ultimately required a total laryngectomy (13).

XXVIII. SARCOMAS OF THE LARYNX

Primary sarcomas of the larynx comprise a rare heterogeneous group of neoplasms that, collectively, compose only 0.3% to 1% of all laryngeal malignancies

(1–3). Any attempt to statistically analyze these tumors is met with frustration, not only because of their rarity, but because many of the cases lack sufficient clinical information, follow-up is incomplete, pathological documentation is often poor, and confusion with spindle cell carcinoma is rampant.

Etiologically, they do not appear to be related to smoking or alcohol intake. Most occur spontaneously, but some are radiation-induced (4). In the study of radiation-induced sarcomas by Kim et al., the median latent periods from radiation exposure to diagnosis of bone and soft tissue sarcomas were, respectively, 11 and 12 years (range 3–20 years) (5). No irradiation tumors were seen in doses below 1100 rets. Exposure to thorium dioxide (Thorotrast) and polyvinyl chloride has also been incriminated in the development of angiosarcomas, especially of the liver. Although patients with neurofibromatosis are at risk for developing malignant schwannomas, these tumors are more commonly located in the deep soft tissues or retroperitoneum and rarely, if ever, in the larynx. Viruses may also be etiologically related to some sarcomas (e.g., kaposi's sarcoma and the HIV).

Grossly, sarcomas, regardless of the putative cell of origin, tend to present as polypoid or multilobulated, firm, submucosal masses that are usually pink, gray, or white. Flat ulcerative or fungating lesions are rare. Multiple biopsies are sometimes necessary to establish the diagnosis. In fact, in the series of Setzen et al., 13% of the patients required more than one biopsy before the diagnosis was established (6). Caution must be particularly exercised in evaluating laryngeal biopsies in patients who have received prior radiation therapy. The distinction between radiation-induced stromal atypia and *de novo* or radiation-induced sarcomas can be difficult, requiring close correlation with the clinical findings and, often, multiple biopsies over a time span to assess the true potential or autonomy of the lesion.

SPCCs of the larynx are also often confused with sarcomas on small biopsies, usually a fibrosarcoma or malignant fibrous histiocytoma. Accordingly, SPCC must always be considered in the differential of all alleged sarcomas of the larynx and excluded by examining multiple histological sections (for the biphasic components), immunohistochemical stains for cytokeratin, or electron microscopy.

Laryngectomy, either partial or total, is the most successful form of therapy (7). Radiation therapy may have merit as an adjunct, but not for primary therapy. The role of chemotherapy is still evolving, but has certainly proved useful in the management of patients with embryonal rhabdomyosarcomas. Metastases are predominantly vascular, usually to the lungs. Involvement of regional lymph nodes is uncommon.

Chondrosarcoma is, by far, the most common sarcoma of the larynx, accounting for almost half of all cases (8). For a more detailed discussion of the clinical and pathological features of the various sarcomas refer to the chapters on bone and soft tissue tumors.

XXIX. SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX

A. Introduction

The hypopharynx, which lies behind the larynx and partially surrounds it on either side, extends from the plane of the hyoid bone superiorly to the lower border of the cricoid cartilage inferiorly (Fig. 105). It consists of three regions: the pyriform sinuses, postcricoid area, and the posterior pharyngeal wall. Although useful for descriptive purposes and classification, these divisions are in continuity with one another and merge with the oropharynx, larynx, and cervical esophagus. The lumen of the hypopharynx is cone-shaped, with a wide opening superiorly and a narrower lumen in the postcricoid and cervical esophageal region.

The hypopharynx is richly endowed with lymphatics that drain primarily to the upper and mid-jugular lymph nodes (1). The lymphatics of the posterior wall also have a significant communication with the retropharyngeal lymph nodes and the node of Rouviere at the base of the skull (2).

The incidence of hypopharyngeal carcinomas more closely parallels the incidence of malignant tumors of the upper gastrointestinal tract, especially the oral cavity rather than the respiratory tract (3). They are only about one-third as common as cancer of the larynx (4).

The distribution of malignant tumors within the hypopharynx varies according to geographic location. In the United States and Canada, approximately 65% to 85% arise in the pyriform sinus, 10% to 20% occur on the posterior wall, and 5% to 15% involve the postcricoid area (4–10) (Fig. 106).

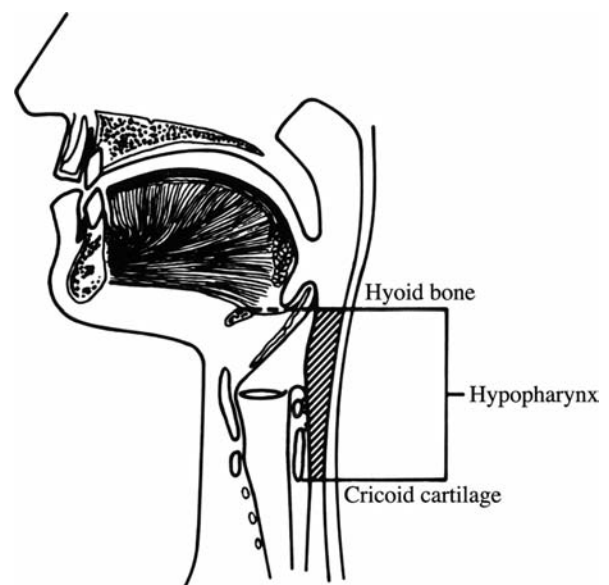


Figure 105. Diagram showing boundaries of the hypopharynx.

DISTRIBUTION AND INCIDENCE OF HYPOPHARYNGEAL CARCINOMAS

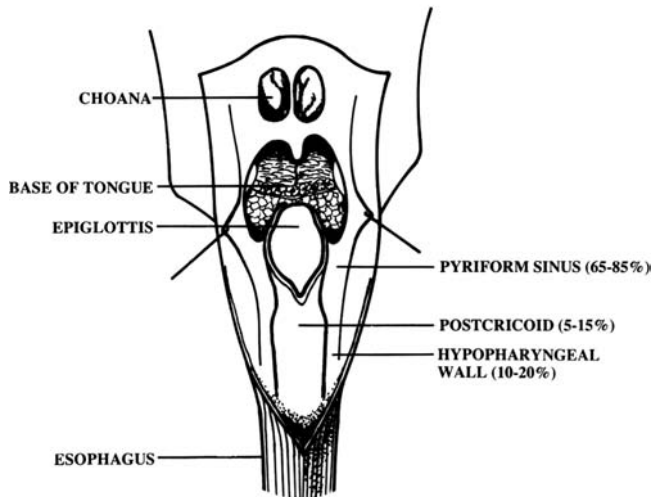


Figure 106. Posterior view of the pharynx showing the distribution and relative frequency of hypopharyngeal carcinomas
Source: From Ref. 11.

B. Etiology

The tumors are etiologically related to smoking, alcohol abuse, and the Plummer–Vinson syndrome (PVS) (4,11–15). There is also evidence that some of the tumors in patients from Japan may be related to the EBV (16).

C. Clinical Features

The peak incidence is in individuals 55 to 65 years of age. Collectively, 80% to 85% of all patients are men, but when specific sites are considered, 50% to 90% of patients with postcricoid carcinomas are women (8,15,17–20). Because the hypopharynx is a clinically “silent” area, patients usually present with advanced tumors. Most are classified as T3 or T4, and 65% to 75% are associated with clinically positive cervical lymph nodes (6,7,10,22,23) (Table 18).

The most common presenting symptoms are dysphagia, sore throat, referred otalgia, hoarseness, sensation of a foreign body in the throat, weight loss, and hemoptysis. Some 20% to 25% of patients complain of only a neck mass (15,17,22).

Pyriform Sinus Carcinoma

The pyriform sinus is shaped like an inverted pyramid or pear. It consists of three walls—anterior, medial, and lateral—that converge inferiorly toward an apex at about the level of the inferior border of the cricoid cartilage. The superior border of the sinus begins at the level of the pharyngoepiglottic fold.

Table 18 T^a Classification of Hypopharyngeal Carcinoma

T1	Tumor limited to one subsite of hypopharynx and ≥ 2 cm in greatest dimension
T2	Tumor involves more than 1 subsite of hypopharynx or an adjacent site, or measures >2 cm but not >4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures >4 cm in greatest dimension or with fixation of hemilarynx
T4	Tumor invades adjacent structures (e.g., thyroid/cricoid cartilage, carotid artery, soft tissues of neck prevertebral fascia/muscles, thyroid and/or esophagus)

^aThe NM classification is similar to that previously given for laryngeal carcinoma; see Table 10.

Source: From Ref. 23.

The medial wall is formed by the posterior surface of the aryepiglottic fold and the arytenoid and cricoid cartilages. The lateral wall consists of the inner surface of the thyroid cartilage and thyrohyoid membrane.

There is no significant lateralization of neoplasms to either the right or left pyriform sinus (24). Because the tumors are often large when discovered, their exact site of origin within the sinus is often difficult to determine (Fig. 107). The tumor may spread medially to invade the lateral wall of the supraglottic larynx (Fig. 108). In this instance, Kirchner indicates that it differs from the usual supraglottic laryngeal carcinoma by growing downward within the paraglottic space to extend beyond the level of the ventricle, thereby behaving more like a transglottic carcinoma (7). It can extend laterally, erode the thyroid cartilage, and directly invade the superior lobe of the thyroid gland. In some instances, the thyroid may be free of contiguous growth, yet contain tumor emboli within lymphatics or blood vessels. Kirchner has noted that when the lateral wall of the sinus is clinically involved, the thyroid cartilage is invaded in 55% of the cases, and when the tumor extends to the apex of the sinus, the cartilage is almost invariably invaded (7). Some tumors may grow superiorly into the base of the tongue or extend across the postcricoid

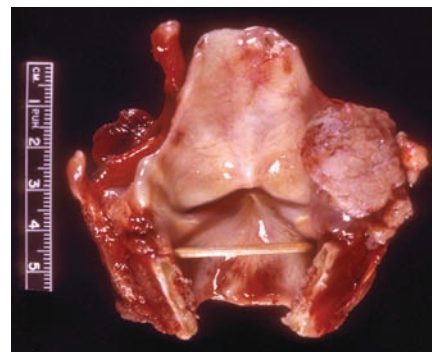


Figure 107. Gross appearance of a squamous cell carcinoma of the right pyriform sinus that also involves the aryepiglottic fold (specimen opened posteriorly).

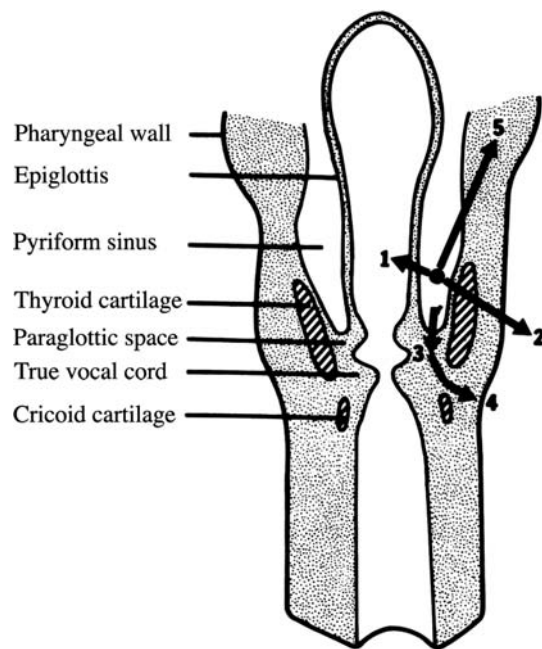


Figure 108. Pyriform sinus cancers may grow medially to involve the supraglottic larynx (1); erode the thyroid cartilage laterally and invade the thyroid gland (2); extend into the paraglottic space (3); and escape through the cricothyroid interspace into the soft tissue of the neck (4); or they may grow superiorly toward the base of the tongue (5). *Source:* From Ref. 11.

area to involve the opposite pyriform sinus or the contiguous posterior pharyngeal wall. Invasion of the cervical esophagus is unusual.

At the time of diagnosis, about 65% to 75% of patients will have positive cervical lymph nodes. However, no more than 10% of patients will present initially with bilateral positive lymph nodes (15,18,24,25).

Posterior Hypopharyngeal Wall Carcinoma

Tumors of the posterior hypopharyngeal wall are three times more common than those of the posterior oropharyngeal wall (26,27). Most studies pertaining to carcinomas of the posterior pharyngeal wall include all levels of the pharynx. This is not unreasonable, for there are no natural anatomical barriers among the three levels of the pharynx (nasopharynx, oropharynx, and hypopharynx) and, at the time of diagnosis, tumors often encroach on or invade more than one level. Furthermore, when posterior pharyngeal wall tumors are divided according to level of occurrence, there are no significant differences in prognosis (26,27).

Almost 80% of these tumors are larger than 5 cm when diagnosed (17). Because these tumors almost invariably cross the midline, a minimum of 10% to

15% of patients will develop bilateral cervical lymph node metastases sometime during the course of their disease (18,28). The lymphatic drainage is primarily to the upper and middle jugular, as well as the retropharyngeal lymph nodes. The retropharyngeal lymph nodes are involved in 42% to 62% of cases and, in 10% of patients, they are the only lymph nodes involved (2,29). In general, however, the incidence of cervical lymph node metastasis from posterior pharyngeal wall cancers is less than that observed in patients with pyriform sinus tumors. The tumors may spread circumferentially to involve the larynx or, in advanced disease, extend into the tonsillar pillars, soft palate, nasopharynx, pyriform sinuses, or cervical esophagus.

Ballantyne indicates that the principal reasons for local recurrence following surgery are (i) failure to remove unrecognized local extension of tumor along muscle or fascial planes or nerves, (ii) failure to eradicate areas of in situ or early invasive cancer, and (iii) implantation of tumor cells in the operative site (29).

Postcricoid Carcinoma

The postcricoid area (the posterior surface of the larynx) extends from the posterior surface of the arytenoid cartilage to the inferior surface of the cricoid cartilage and is bounded laterally by the pyriform sinuses (3). There is marked geographic variation in the incidence of postcricoid carcinomas (PCC). They are especially common in Scandinavian countries where PVS was at one time prevalent; the syndrome is now being recognized earlier and treated accordingly (20). PVS, also known as Paterson-Kelly syndrome and sideropenic dysphagia, is characterized predominantly by dysphagia, iron-deficiency anemia, glossitis, cheilitis, and achlorhydria. The dysphagia is due to webs, stenosis, or mucosal atrophy. The webs most often arise from the anterior esophageal wall just distal to the cricoid cartilage. When carcinoma develops, it arises immediately proximal to the webs and not within them (14). In the past, of those patients with PCC, 30% to 70% have also had PVS (13,19,30,31). Conversely, of those patients with PVS, only 1% to 10% have developed carcinoma (13,30). Richards et al. have observed that the peak incidence of PCC occurs 15 years later than the peak incidence of PVS (31).

Food stasis secondary to webs or stricture may partly explain the increased incidence of carcinoma in this site (14). Because the webs have been noted to decrease or even disappear with dietary supplements, particularly iron, early recognition, and therapy are mandatory to lessen the incidence of this lethal tumor. In addition to the postcricoid area, patients with PVS may develop tumors in other mucosal sites, especially the oral cavity and esophagus (13).

Postcricoid carcinomas commonly invade the cricoid cartilage and cricoarytenoid muscle. They frequently become circumferential, and may extend through the muscular lateral walls to directly invade the thyroid gland. Such behavior may warrant the need for partial or total thyroidectomy (32). In the surgical treatment of PCC, Harrison indicates that the superior extent of the disease is technically

not difficult to excise, but extension inferiorly can be, for the disease has tendency to involve the party wall between the esophagus and trachea, necessitating removal of a considerable length of trachea (21). The lymphatic drainage is mainly to the middle and lower jugular chain and to the paratracheal nodes (18,33). Eighteen percent of patients have or will develop bilateral cervical lymph node metastasis (18). However, it is unrecognized involvement of the paratracheal nodes that is responsible for most local recurrences (33). Metastasis to these nodes may also secondarily involve the thyroid.

D. Treatment and Prognosis

Treatment of hypopharyngeal carcinoma depends on the patient's general state of health, location and extent of the tumor, and the technical ability of the surgeon. Any therapeutic regimen, however, that fails to consider the following is doomed to failure:

1. Tumors in this region are notorious for growing beneath an intact mucosa, extending far beyond their clinically apparent margins. The average extent of submucosal spread is 10 mm (34).
2. A total of 65% to 75% of patients have positive ipsilateral cervical lymph nodes at the time of diagnosis, and 10% to 20% will either have or develop contralateral nodal metastases (3,5,7,15,18,21,24,25,28,35–37). Furthermore, 10% to 60% of patients with clinically negative cervical lymph nodes can be expected to harbor occult metastases (5,7,15).
3. The retropharyngeal and paratracheal lymph nodes must be considered, respectively, when dealing with posterior pharyngeal wall and post-cricoid carcinomas.
4. Because as many as 17% of all hypopharyngeal carcinomas may involve the thyroid, some form of thyroidectomy may be required (3,32).
5. Clinically, 20% to 40% of patients either have or will develop systemic metastases (6,15,22,38,39). The median time from diagnosis to detection of metastasis is nine months (6). The most common sites are the lungs, mediastinum, brain, bones, and liver.
6. Approximately 15% (range 7–31%) of these individuals have multiple primary malignancies (6,15,18,24,26,29). Thirty-five percent of the second primaries are diagnosed before, 25% synchronous with, and 40% subsequent to the discovery of the hypopharyngeal carcinoma (6,18). They are most often found in the head and neck, lung, esophagus, colon, or rectum.

Details of therapy have been adequately covered by others (4,5,7,8,15,17–19,22,25,28,29,32,33,38–54). In general, T1S, T1, some T2, and advanced inoperable lesions can be treated with irradiation, either curatively or palliatively. Other tumors are approached surgically in conjunction with pre- or postoperative radiotherapy. Although most deaths are due to uncontrolled local disease, the relative high incidence of distant metastases

warrants consideration of adjuvant chemotherapy (15). Eighty percent of recurrences manifest within two years of treatment (25,40). Of those patients dying of disease, almost half do so within the year following diagnosis (6,25,33). When all three sites of the hypopharynx are considered collectively, the overall five-year survival rate is between 20% and 40% (4,5,8,15,17–20,22,24,41,43,50,51,54). If only pyriform sinus tumors are considered, some recent studies indicate a better survival. Spector et al. reviewed 408 squamous carcinoma of the pyriform sinus and observed the 5-, 10-, 15-, and 20-year cumulative survival rates to be, respectively, 56, 35, 31, and 20% (55). If the tumor involved only one wall of the pyriform sinus, the five-year survival was 53%, compared with 63% for tumors that involved the medial wall, aryepiglottic fold, or supraglottic larynx, and 49% for tumors that involved two or three walls of the sinus with extension to the pyriform apex or postcricoid region.

XXX. TUMORS OF THE TRACHEA

A. Introduction

Primary tumors of the trachea are rare, with a reported frequency of less than 0.2 per 100,000 persons per year and a prevalence of 1 per 15,000 autopsies (1).

The ratio of benign to malignant tumors varies according to age. In children, 60% to 90% of all tracheal tumors are benign and the most frequent are squamous papillomas, hemangiomas, and granular cell tumors (2,3). Of the remaining 10% to 40% that are malignant, malignant fibrous histiocytoma and mucoepidermoid carcinoma predominate (3). In contrast, in adults almost 90% of primary tracheal neoplasms are malignant and the two most common, by far, are squamous cell carcinoma and adenoid cystic carcinoma (4). These two tumors together comprise about 70% of all primary tracheal neoplasms in adults. Whether squamous cell carcinoma or adenoid cystic carcinoma is the more common depends on the series. In a collective review of 766 adult tracheal tumors, we observed 51% to be squamous cell carcinomas and 21% adenoid cystic carcinomas (4–7).

Currently, there is no TMN staging system for tracheal tumors.

B. Anatomy

The trachea extends from the lower border of the cricoid cartilage to the carina and averages 11 cm in length in the adult, varying roughly in proportion to the height of the individual (8,9) (Fig. 109). It is 2.0 to 2.7 cm in transverse dimension and 1.6 to 2.0 in sagittal diameter (10). There are approximately two tracheal cartilaginous rings per centimeter of trachea, with a total number of about 18 to 22. The tracheal cartilages are connected one to another by fibroelastic annular ligaments. In a few instances, the first tracheal ring may be fused to the cricoid cartilage.

The trachea is continuous with the larynx superiorly and the bronchi inferiorly. Anteriorly it is

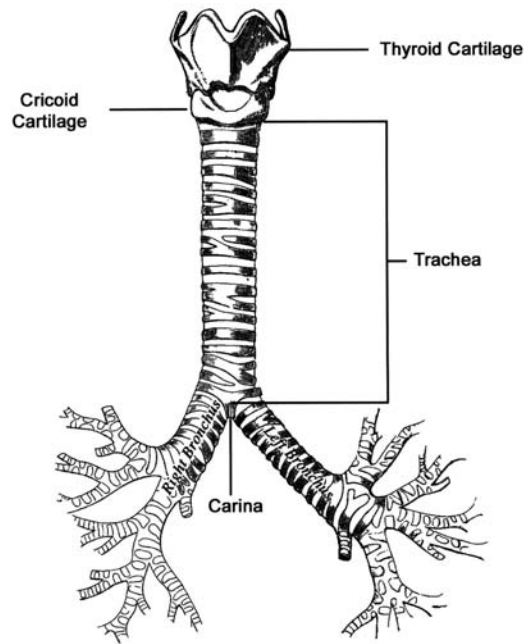


Figure 109. Anatomic boundaries of the trachea.

intimately associated with the thyroid gland and posteriorly with the esophagus.

The trachea is lined entirely by ciliated respiratory epithelium and contains abundant mucoserous glands in the lamina propria. Although usually referred to as rings, the cartilages are incomplete posteriorly and form only about two-third of a circle. The posterior noncartilaginous area, referred to as the membranous portion, contains prominent smooth muscle. The submucosal lymphatics drain toward the posterior part of the trachea and connect with the paratracheal lymph nodes. They also anastomose with subcarinal, peribronchial, and esophageal lymph nodes (10).

C. Squamous Cell Carcinoma

Squamous cell carcinoma of the trachea occurs primarily in older individuals, usually in the sixth or seventh decade of life (mean age 65, range 25–83 years) (4,6,) (Fig. 110). The gender distribution ranges from equal to 3:1 in favor of males. Most are heavy smokers.

Signs and symptoms include airway compromise, cough, hemoptysis, hoarseness, fever, weight loss, wheezing, and, infrequently, superior vena cava syndrome. A delay in diagnosis of months to even a year or more is not uncommon. This is due, in part, to the fact that the symptoms are often mistaken for asthma and that 50% occlusion of the airway is necessary to produce dyspnea on exertion and 75% occlusion to produce dyspnea at rest (11). As a result, tumors greater than 2 cm in greatest dimension are

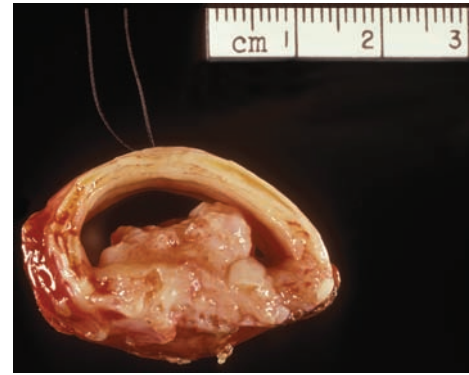


Figure 110. Cross section of a squamous cell carcinoma of the trachea with a predominant intraluminal growth.

commonly observed at diagnosis and about 35% are associated with positive cervical lymph nodes (11).

According to Gelder and Hetzel, 45% of all squamous cell carcinomas are found in the lower one-third of the trachea, 32% in the upper one-third, and 15% in the middle third; in the remaining 8%, the tumors were extensive and involved multiple sites (6).

Surgical excision followed by radiation and/or chemotherapy offers the best chance for cure (4,6,7,11–16). Distant metastases to lungs, cervical lymph nodes, liver, and bones are common. Gelder and Hetzel observed an overall 25% five-year survival rate in their review of 174 squamous cell carcinoma of the trachea (6). Tumors associated with negative lymph nodes and tumor-free margins that originate in the upper trachea and are less than 2 cm in size have the best prognosis.

D. Adenoid Cystic Carcinoma

Adenoid cystic carcinoma of the trachea, in contrast to squamous cell carcinoma, occurs in a younger age group (mean 45–50 years, range 15–80 years), exhibits an equal gender distribution and is not as strongly associated with smoking (1,4,6). Symptoms are similar but of much longer duration, averaging 15 months before diagnosis.

In a review of 29 cases, Gelder and Hetzel observed an equal distribution between the upper, mid and lower thirds of the trachea (6). Extension beyond the wall of the trachea is almost universal (1).

Surgical resection, often augmented with adjuvant radiation, offers the best chance for cure. Survival rates at 5 years range from 65% to 80% and, at 10 years 50% to 60% (1,6). In a follow-up of 38 cases, Maziak et al. observed a local recurrence of 21%, regional lymph node involvement in 19% and hematogenous (distant) metastases in 44%, especially to the lungs (1). Patients with positive resection margins and even distant metastasis may still experience long-term palliation.

XXXI. METASTASES TO THE LARYNX, HYPOPHARYNX AND TRACHEA

A. Introduction

Metastases to the larynx are uncommon. Batsakis et al. observed only 11 cases over a 20-year interval at the M.D. Anderson Hospital in Houston, Texas (1). Ferlito identified eight additional cases in a series of more than 4000 malignant neoplasms of the larynx at the University of Padua, Italy (2). In 1993, only 134 cases were recorded in the world literature (2). Metastases to the hypopharynx and trachea are even more unusual.

Laryngeal metastases increase with age (median 58 years, range 24 to 83 years) and are more common in males by a ratio of 2:1 (1). The overwhelming majority of tumors that metastasize to the larynx are either malignant melanomas or carcinomas (Table 19). Only 5% or less are from mesenchymal tumors (bone and soft tissue sarcomas).

The sites of origin of 12 tumors metastatic to the trachea are shown in Table 20.

Metastases to the larynx may be submucosal, cartilaginous, or both. If cartilage is involved, it is usually only in the portion that has undergone ossification (Fig. 111).

The most frequently affected site is the supraglottis (35–40% of all cases) followed by the subglottis (10–20%) and glottis (5–10%). Synchronous involvement of multiple laryngeal sites, however, is common and observed in about 35% of all cases (1,3).

The pyriform sinus is the most frequent site of metastasis in the hypopharynx.

The majority of metastases to the larynx are through the systemic circulation, often following the route of the inferior vena cava, right heart, lungs, left heart, aorta, external carotid artery, superior thyroid artery and laryngeal artery. Spread may also take place via the retrograde circulation of the paravertebral venous

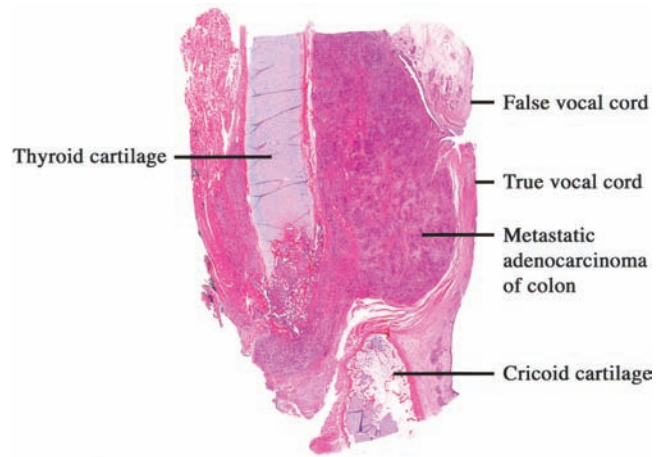


Figure 111. Adenocarcinoma of the colon metastatic to the larynx. Source: Courtesy of Mona Melhem, M.D, VA Hospital, Pittsburgh, PA.

plexus or thoracic lymphatic duct. The infrequent occurrence of metastases to the larynx may therefore be related to the terminal location of the larynx in the lymphatic-vascular circulation. Known differences in regional lymphatic and vascular supply of the larynx determine the distribution of metastases within the larynx.

B. Clinical Features

The signs and symptoms of metastatic tumors are similar to those exhibited by primary tumors of the larynx and vary according to location. Supraglottic lesions present with a sensation of a foreign body in the throat, dysphagia, or a change in quality of the voice, while glottic deposits manifest as hoarseness, and subglottic lesions as compromise of the airway. Richly vascular tumors, such as renal cell carcinomas and thyroid carcinomas, often result in hemoptysis. On rare occasions, the metastasis is the only evidence of an otherwise occult primary tumor.

Tracheal metastases result in cough, stridor, wheezing, dyspnea, and/or hemoptysis.

C. Prognosis

Metastases to the larynx, trachea, or hypopharynx are usually associated with terminal, widespread disseminated disease. In some instances, the metastasis may be isolated or localized and, with appropriate therapy, a prolonged survival can be achieved.

Table 19 Site of Origin of 120 Tumors Metastatic to Larynx

Site	Frequency (%)
Skin (melanoma)	39.1
Kidney	13.3
Breast	9.2
Lung	7.5
Prostate	6.7
Colon	3.3
Stomach	2.5
Miscellaneous	18.4

Source: Based on Ref. 3.

Table 20 Site of Origin of 12 Tumors Metastatic to Trachea

Site	Frequency (%)
Breast	33
Colon	25
Skin (melanoma)	17
Uterine cervix	8
Endometrium	8
Ovary	8

Source: Based on Refs. (4–9)

REFERENCES

I. VOCAL CORD NODULES AND POLYPS

1. Dikkers FG, Nikkels PGJ. Benign lesions of the vocal folds: Histopathology and phonotrauma. *Ann Otol Rhinol Laryngol* 1995; 104:698–703.

2. Lancer J, Syder D, Jones AS, et al. Vocal cord nodules: a review. *Clin Otolaryngol Allied Sci* 1988; 13:43–51.
 3. Marcotullio D, Magliulo G, Pietrunti S, et al. Exudative laryngeal diseases of Reinke's space: a clinicohistopathological framing. *J Otolaryngol* 2002; 31:376–380.
 4. Wallis L, Jackson-Menaldi C, Holland W, et al. Vocal fold nodule vs. vocal fold polyp: answer from surgical pathologist and voice pathologist point of view. *J Voice* 2004; 18:125–129.
 5. Johns MM. Update on the etiology, diagnosis, and treatment of vocal fold nodules, polyps and cysts. *Curr Opin Otolaryngol Head Neck Surg* 2003; 11:456–461.
 6. Zeitels SM, Casiano RR, Gardner GM, et al. Management of common voice problems: Committee report. *Otolaryngol Head Neck Surg* 2002; 126:333–348.
 7. Tillman B, Rudert H, Schunke M, et al. Morphological studies on the pathogenesis of Reinke's edema. *Eur Arch Otorhinolaryngol* 1995; 252:469–474.
 8. Courey MS, Shohet JA, Scott MA, et al. Immunohistochemical characterization of benign laryngeal lesions. *Ann Otol Rhinol Laryngol* 1996; 105:525–531.
 9. Thibeault SL, Gray SD, Li W, et al. Genotypic and phenotypic expression of vocal fold polyps and Reinke's edema: A preliminary study. *Ann Otol Rhinol Laryngol* 2002; 111:302–309.
 10. Kambic V, Radsel Z, Zargi M, et al. Vocal cord polyp: incidence, histology, and pathogenesis. *J Laryngol Otol* 1981; 95:609–618.
 11. Kleinsasser O. Pathogenesis of vocal cord polyps. *Ann Otol Rhinol Laryngol* 1982; 91:378–381.
 12. Sena T, Brady MS, Huvos AG, et al. Laryngeal myxoma. *Arch Otolaryngol Head Neck Surg* 1991; 117:430–432.
 13. Lancer JM, Syder D, Jones AS, et al. The outcome of different management patterns for vocal cord nodules. *J Otolaryngol Otol* 1988; 102:423–427.
- ## II. CONTACT ULCER, CONTACT GRANULOMA, INTUBATION GRANULOMA
1. Howland WS, Lewis JS. Mechanisms in the development of post-intubation granulomas of the larynx. *Ann Otol Rhinol Laryngol* 1986; 65:1006–1011.
 2. Donnelly WH. Histopathology of endotracheal intubation. An autopsy study of 99 cases. *Arch Pathol* 1969; 88: 511–520.
 3. Burns HP, Dayal VS, Scott A, et al. Laryngotracheal trauma: observations on its pathogenesis and its prevention following prolonged orotracheal intubation in the adult. *Laryngoscope* 1979; 90:1316–1325.
 4. Balestrieri F, Watson CB. Intubation granuloma. *Otolaryngol Clin North Am* 1982; 15:567–579.
 5. Bain WM, Harrington JW, Thomas LE, et al. Head and neck manifestations of gastroesophageal reflux. *Laryngoscope* 1983; 93:175–179.
 6. Feder RJ, Michell MJ. Hyperfunctional, hyperacidic, and intubation granulomas. *Arch Otolaryngol* 1984; 110: 582–584.
 7. Benjamin B, Croxson G. Vocal cord granulomas. *Ann Otol Rhinol Laryngol* 1985; 94:538–541.
 8. Wilson JA, White A, von Haacke NP, et al. Gastroesophageal reflux and posterior laryngitis. *Ann Otol Rhinol Laryngol* 1989; 98:405–410.
 9. Drosnes DL, Zwillenberg DA. Laryngeal granulomatous polyp after short-term intubation of a child. *Ann Otol Rhinol Laryngol* 1990; 99:183–186.
 10. Wenig BM, Heffner DK. Contact ulcers of the larynx. A reacquaintance with the pathology of an often underdiagnosed entity. *Arch Pathol Lab Med* 1990; 114:825–828.
 11. Benjamin B, Roche J. Vocal granuloma including sclerosis of the arytenoid cartilage: radiographic findings. *Ann Otol Rhinol Laryngol* 1993; 102:756–760.
 12. Olson NR. Laryngopharyngeal manifestations of gastroesophageal reflux disease. *Otolaryngol Clin North Am* 1991; 24:1201–1213.
 13. Maronion N, Haggitt R, Oelschlager BK, et al. Histologic features of reflux-attributed laryngeal lesions. *Am J Med* 2003; 115(suppl 3):1055–1085.
 14. Vaezi MF. Gastroesophageal reflux disease and the larynx. *J Clin Gastroenterol* 2003; 36:198–203.
 15. Devanery KO, Rinaldo A, Ferlito A. Vocal process granuloma of the larynx—recognition, differential diagnosis and treatment. *Oral Oncol* 2005; 41:666–669.
 16. Jecker P, Orloff LA, Mann WJ. Extraesophageal reflux and upper aerodigestive tract disease. *ORL* 2005; 67:185–191.
 17. Fechner RE, Cooper PH, Mills SE. Pyogenic granuloma of the larynx and trachea. A causal and pathologic misnomer for granulation tissue. *Arch Otolaryngol* 1981; 107:30–32.
- ## III. TEFLON GRANULOMA (TEFLONOMA)
1. Maran AGD, Hardcastle PF, Hamid A, et al. An Analysis of 102 cases of polytef injection of the vocal cord. *J Laryngol Otol* 1986; 100:47–51.
 2. McCaffrey TV. Transcutaneous Teflon injection for vocal cord paralysis. *Otolaryngol Head Neck Surg* 1993; 109: 54–59.
 3. Lewy RB. Teflon injection: pointers and pitfalls. *Ann Otol Rhinol Laryngol* 1993; 102:283–284.
 4. Dedo HH, Carlsoo B. Histologic evaluation of Teflon granulomas of human vocal cords. A light and electron microscopic study. *Acta Otolaryngol* 1982; 93:475–484.
 5. Ossoff RH, Koriwchak MJ, Nettekville JL, et al. Difficulties in endoscopic removal of Teflon granulomas of the vocal fold. *Ann Otol Rhinol Laryngol* 1993; 102:405–412.
 6. Lewy RB, Millet D. Immediate local tissue reaction to Teflon vocal cord implants. *Laryngoscope* 1978; 88: 1339–1342.
 7. Wenig BM, Heffner DK, Oertel YC, et al. Teflonomas of the larynx and neck. *Hum Pathol* 1990; 21:617–623.
 8. Kirchner FR, Toledo PS, Sovoboda DJ. Studies of the larynx after Teflon injection. *Arch Otolaryngol* 1966; 83:350–354.
 9. Lewy RB. Experience with vocal cord injection. *Ann Otol Rhinol Laryngol* 1976; 85:440–450.
 10. Lewy RB. Teflon injection of the vocal cord: complications, errors and precautions. *Ann Otol Rhinol Laryngol* 1983; 92:473–474.
 11. Dedo HH, Urrea RD, Lawson L. Intracordal injection of Teflon in the treatment of 135 patients with dysphonia. *Ann Otol Rhinol Laryngol* 1973; 82:661–667.
 12. Rubin JH. Misadventures with injectable polytef (Teflon). *Arch Otolaryngol* 1975; 101:114–116.
 13. Nakayama M, Ford CN, Bless DM. Teflon vocal fold augmentation: failures and management in 28 cases. *Otolaryngol Head Neck Surg* 1993; 109:493–498.
 14. Stephens CB, Arnold GE, Stone JW. Larynx injected with polytef paste. *Arch Otolaryngol* 1976; 102:432–435.
 15. Ellis JC, McCaffrey TV, DeSanto LW. Migration of Teflon after vocal cord injection. *Otolaryngol head Neck Surg* 1987; 96:63–66.
 16. Vavares MA, Montgomery WW, Hillman RE. Teflon granuloma of the larynx: Etiology, pathophysiology, and management. *Ann Otol Rhinol Laryngol* 1995; 104: 511–515.

IV. SUBGLOTTIC STENOSIS

1. Quiney RE, Gould SJ. Subglottic stenosis: a clinicopathological study. *Clin Otolaryngol* 1985; 10:315–327.
2. Grundfast KM, Morris MS, Bernsky C. Subglottic stenosis: retrospective analysis and proposal for standard reporting system. *Ann Otol Rhinol Laryngol* 1987; 96:101–105.
3. McCaffrey TV. Management of subglottic stenosis in the adult. *Ann Otol Rhinol Laryngol* 1991; 100:90–94.
4. Park SS, Streitz JM, Rebeiz EE, et al. Idiopathic subglottic stenosis. *Arch Otolaryngol Head Neck Surg* 1995; 121:894–897.
5. Grillo HC, Mark EJ, Mathisen DJ, et al. Idiopathic laryngotracheal stenosis and its management. *Ann Thorac Surg* 1993; 56:80–87.
6. de Vries N, Gans ROB, Donker AJM, et al. Autoantibodies against constituents of neutrophils in the diagnosis and treatment of isolated subglottic stenosis. *Arch Otolaryngol Head Neck Surg* 1992; 118:1120–1123.

V. TRACHEOPATHIA OSTEOCHONDROPLASTICA

1. Harma RA, Suukari S. Tracheopathic chondro-osteoplastica. A clinical study of thirty cases. *Acta Otolaryngol* 1977; 84:118–123.
2. Pounder DJ, Pieterse AS. Tracheopathia osteoplastica: report of four cases. *Pathology* 1982; 14:429–433.
3. Young RH, Sandstrom RE, Mark GJ. Tracheopathia osteoplastica. Clinical, radiological, and pathological correlations. *J Thorac Cardiovasc Surg* 1980; 79:537–541.
4. Paaske PB, Tang E. Tracheopathia osteoplastica in the larynx. *J Laryngol Otol* 1985; 99:305–310.
5. Hirsch M, Tovi F, Goldstein J, et al. Diagnosis of tracheopathia osteoplastica by computed tomography. *Ann Otol Rhinol Laryngol* 1985; 94:217–219.
6. Prakash UBS, McCullough AE, Edell ES, et al. Tracheopathia osteoplastica. Familial occurrence. *Mayo Clin Proc* 1989; 64:1091–1096.
7. Nienhuis DM, Prakash UBS, Edell ES. Tracheobronchopathia osteochondroplastica. *Ann Otol Rhinol Laryngol* 1990; 99:689–694.
8. Birzgalis AR, Farrington WT, O'Keefe L, et al. Localized tracheopathic osteoplastica of the subglottis. *J Laryngol Otol* 1993; 107:352–353.
9. Tibesar RJ, Edell ES. Tracheopathia osteoplastica: Effective long-term management. *Otolaryngol Head Neck Surg* 2003; 129:303–304.
10. Grillo HC, Wright CD. Airway obstruction owing to tracheopathia osteoplastica: treatment by linear tracheoplasty. *Ann Thorac Surg* 2005; 79:1676–1681.
11. Mboti FB, Ninane V, Larsimont D, et al. Acute respiratory failure from tracheopathia osteoplastica 2005; 105:227–228.
12. Jepsen O, Sorensen H. Tracheopathia osteoplastica and ozaena. *Acta Otolaryngol (Stockh)*. 1960; 51:79–83.
13. Eimind K. Tracheopathia chondro-osteoplastica. *Nord Med* 1964; 72:1029–1031.

VI. CYSTS AND LARYNGOCELES

1. Delahunty JE, Cherry J. The laryngeal saccule. *J Laryngol Otol* 1969; 83:803–815.
2. Broyles, EN. Anatomical observations concerning the laryngeal appendix. *Ann Otol Rhinol Laryngol* 1959; 68: 461–470.
3. Hollinger LD, Barnes DR, Smid LJ. Laryngocele and saccular cysts. *Ann Otol Rhinol Laryngol* 1978; 87:675–685.

4. DeSanto LW. Laryngocele, laryngeal mucocele, large saccules, and laryngeal saccular cysts: a developmental spectrum. *Laryngoscope* 1974; 84:1291–1296.
5. DeSanto LW, Devine KD, Weiland LH. Cysts of the larynx—classification. *Laryngoscope* 1970; 80:145–176.
6. Newman BH, Taxy JB, Laker HI. Laryngeal cysts in adults: a clinicopathologic study of 20 cases. *Am J Clin Pathol* 1984; 81:715–720.
7. Ramesar K, Albizzati C. Laryngeal cysts: a clinical relevance of a modified working classification. *J Laryngol Otol* 1988; 102:923–925.
8. Donegan JO, Strife JL, Seid AB, et al. Internal laryngocele and saccular cysts in children. *Ann Otol Rhinol Laryngol* 1980; 89:409–413.
9. Bouchayer M, Cornut G, Witzig E, et al. Epidermoid cysts, sulci, and mucosal bridges of the true vocal cord: a report of 157 cases. *Laryngoscope* 1985; 95:1087–1094.
10. Niparko JK, Moran ML, Baker SR. Laryngeal saccular cysts: an unusual clinical presentation. *Otolaryngol Head Neck Surg* 1987; 97:576–579.
11. Milutinovic Z, Vasiljevic J. Contribution to the understanding of the etiology of vocal fold cysts: a functional and histologic study. *Laryngoscope* 1992; 102:568–571.
12. Mitchell DB, Irwin BC, Bailey CM, et al. Cysts of the infant larynx. *J Laryngol Otol* 1987; 101:833–837.
13. Smith JD, Cotton R, Meyer CM III. Subglottic cysts in the premature infant. *Arch Otolaryngol Head Neck Surg* 1990; 116:479–482.
14. Civantos FJ, Holinger LD. Laryngoceles and saccular cysts in infants and children. *Arch Otolaryngol Head Neck Surg* 1992; 118:296–300.
15. Weber PC, Kenna MA, Casselbrant ML. Laryngeal cysts: a cause of neonatal airway obstruction. *Otolaryngol Head Neck Surg* 1993; 109:129–134.
16. Myssiorek D, Persky M. Laser endoscopic treatment of laryngoceles and laryngeal cysts. *Otolaryngol Head Neck Surg* 1989; 100:538–541.
17. Micheau C, Luboinski B, Lanchi P, et al. Relationship between laryngoceles and laryngeal carcinomas. *Laryngoscope* 1978; 88:680–688.
18. Canalis RF, Maxwell DS, Hemenway WC. Laryngocele—an updated review. *J Otolaryngol* 1977; 6:191–199.
19. Macfie, WCDD. Asymptomatic laryngoceles in wind instrument bandmen. *Arch Otolaryngol* 1966; 83:270–275.
20. Baker HL, Baker SR, McClatchey KD. Manifestations and management of laryngoceles. *Head Neck Surg* 1982; 4: 450–456.
21. Close LG, Merker M, Burns DK, et al. Asymptomatic laryngocele: incidence and association with cancer. *Ann Otol Rhinol Laryngol* 1987; 96:393–299.
22. Holinger PH, Brown WT. Congenital webs, cysts, laryngoceles, and other anomalies of the larynx. *Ann Otol Rhinol Laryngol* 1976; 76:744–752.
23. Meda P. Symptomatic Laryngocele in cancer of the larynx. *Arch Otolaryngol* 1952; 56:512–520.
24. Canalis RF. Observations on the simultaneous occurrence of laryngocele and cancer. *J Otolaryngol* 1976; 5:207–212.
25. Birt D. Observations on the size of the saccule in laryngectomy specimens. *Laryngoscope* 1987; 97:190–200.
26. Celin SE, Johnson J, Curtin H, et al. The association of laryngoceles with squamous cell carcinoma of the larynx. *Laryngoscope* 1991; 101:529–536.

VII. PAPILLOMAS

1. Myers JN, Myers EN, Barnes L. Benign neoplasms of the larynx. In: Fried MP, ed. *The Larynx: A Multidisciplinary Approach*. 2nd ed. Chicago: Mosby-Yearbook, 1996:443–459.

2. Capper JWR, Bailey CM, Michaels L. Squamous papillomas of the larynx in adults. A review of 63 cases. *Clin Otolaryngol* 1983; 8:109-119.
3. Lindeberg H, Oster S, Oxlund I, et al. Laryngeal papillomas: classification and course. *Clin Otolaryngol* 1986; 11:423-429.
4. Benjamin B, Parsons DS. Recurrent respiratory papillomatosis: a 10 year study. *J Laryngol Otol* 1988; 102:1022-1028.
5. Lindeberg H, Elbrond O. Laryngeal papillomas: clinical aspects in a series of 231 patients. *Clin Otolaryngol* 1989; 14:333-342.
6. Quiney RE, Hall D, Croft CB. Laryngeal papillomatosis: analysis of 113 patients. *Clin Otolaryngol* 1989; 14:217-225.
7. Hartley C, Hamilton J, Birzgalis AR, et al. Recurrent respiratory papillomatosis—the Manchester experience, 1974-1992. *J Laryngol Otol* 1994; 108:226-229.
8. Kleinsasser O, Cruz GD. Juvenile and adult papillomas of the larynx. *Excerpta Medica* 1974; 28:23 (abstr).
9. Batsakis JG, Raymond AK, Rice DH. The pathology of head and neck tumors: papillomas of the upper aerodigestive tract, part 18. *Head Neck Surg* 1983; 5:332-344.
10. Ullmann EV. On the etiology of laryngeal papilloma. *Acta Otolaryngol* 1923; 5:317-334.
11. Lack EE, Jenson AB, Smith HG, et al. Immunoperoxidase localization of human papillomavirus in laryngeal papillomas. *Intervirology* 1980; 14:148-154.
12. Tsutsumi K, Nakajima T, Gotoh M, et al. In situ hybridization and immunohistochemical study of human papillomavirus infection in adult laryngeal papillomas. *Laryngoscope* 1989; 99:80-85.
13. Terry RM, Lewis FA, Robertson S, et al. Juvenile and adult laryngeal papillomata: classification by in-situ hybridization for human papillomavirus. *Clin Otolaryngol* 1989; 14:135-139.
14. Levi JE, Delcelo R, Alberti VN, et al. Human papillomavirus DNA in respiratory papillomatosis detected by in situ hybridization and the polymerase chain reaction. *Am J Pathol* 1989; 135:1179-1184.
15. Lindeberg H, Johansen L. The presence of human papillomavirus (HPV) in solitary adult laryngeal papillomas demonstrated by in-situ DNA hybridization with sulphonated probes. *Clin Otolaryngol* 1990; 15:367-371.
16. Rimell F, Maisel R, Dayton V. In situ hybridization and laryngeal papillomas. *Ann Otol Rhinol Laryngol* 1992; 101:119-126.
17. Rihkanen H, Aaltonen L-M, Syrjanen SM. Human papillomavirus in laryngeal papillomas and in adjacent normal epithelium. *Clin Otolaryngol* 1993; 18:470-474.
18. Holinger PH, Shipkowitz NL, Holper JC, et al. Studies of etiology of laryngeal papilloma and an autogenous laryngeal papilloma vaccine. *Acta Otolaryngol* 1968; 65:63-69.
19. Boyle WF, McCoy EG, Fogarty WA. Electron microscopic identification of virus-like particles in laryngeal papilloma. *Ann Otol Rhinol Laryngol* 1971; 80:693-698.
20. Cook TA, Cohn AM, Brunschwig JP, et al. Laryngeal papilloma: etiologic and therapeutic considerations. *Ann Otol Rhinol Laryngol* 1971; 82:649-698.
21. Strong MS, Vaughn CW, Healy GB, et al. Recurrent respiratory papillomatosis. Management with the CO2 laser. *Ann Otol Laryngol* 1976; 85:508-516.
22. Incze JS, Lui PS, Strong MS, et al. The morphology of human papillomas of the upper respiratory tract. *Cancer* 1977; 39:1634-1646.
23. Quick CA, Watts SL, Krzyzek RA, et al. Relationship between condylomata and laryngeal papillomata. Clinical and molecular virological evidence. *Ann Otol Rhinol Laryngol* 1980; 89:467-471.
24. Bennett RS, Powell KR. Human papillomaviruses: association between laryngeal papillomas and genital warts. *Pediatr Infect Dis J* 1987; 6:229-232.
25. Abramson AL, Steinberg BM, Winkler B. Laryngeal papillomatosis: clinical, histopathologic and molecular studies. *Laryngoscope* 1987; 97:678-685.
26. Kashima HK, Shah F, Lyles A, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent papillomatosis. *Laryngoscope* 1992; 102:9-13.
27. Silverberg MJ, Thorsen P, Lindeberg H, et al. Condyloma in pregnancy is strongly predictive of juvenile recurrent respiratory papillomatosis. *Obstet Gynecol* 2003; 101:645-652.
28. Silverberg, MJ, Thorsen P, Lindeberg H, et al. Clinical course of recurrent respiratory papillomatosis in Danish children. *Arch Otolaryngol Head Neck Surg* 2004; 130:711-716.
29. Shykhom M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clin Otolaryngol Allied Sci* 2002; 27:237-243.
30. Shah K, Kashima H, Polk BF, et al. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obstet Gynecol* 1986; 68:795-799.
31. Kosko JR, Derkay CS. Role of cesarean section in prevention of recurrent respiratory papillomatosis – Is there one? *Int J Pediatr Otorhinolaryngol* 1996; 35:31-38.
32. Wiatrak BJ, Wiatrak DW, Broker TR, et al. Recurrent respiratory papillomatosis: A longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. *Laryngoscope* 2004; 114(suppl 104):1-22.
33. Hallmo P, Naess O. Laryngeal papillomatosis with human papillomavirus DNA contracted by a laser surgeon. *Eur Arch Otorhinolaryngol* 1991; 248:425-427.
34. Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. *Arch Pathol Head Neck Surg* 1995; 121:1386-1391.
35. Reeves WC, Ruparel SS, Swanson KI, et al. National registry for juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg* 2003; 129:976-982.
36. Wiatrak BJ. Overview of recurrent papillomatosis. *Curr Opin Otolaryngol Head Neck Surg* 2003; 11:433-441.
37. Silverman DA, Pitman MJ. Current diagnostic and management trends for recurrent respiratory papillomatosis. *Curr Opin Otolaryngol Head Neck Surg* 2004; 12:532-537.
38. Lee JH, Smith RJ. Recurrent respiratory papillomatosis: pathogenesis to treatment. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13:354-359.
39. Holinger PH, Johnston KC, Anison GC. Papilloma of the larynx: a review of 109 cases with preliminary report of Aureomycin therapy. *Ann Otol Rhinol Laryngol* 1950; 59:547-564.
40. Al-Saleem T, Peale AG, Norris CM. Multiple papillomatosis of the lower respiratory tract: clinical and pathological study of eleven cases. *Cancer* 1968; 22:1173-1184.
41. Lynn RB, Takita H. Tracheal papilloma: case report and review of the literature. *Can Med Assoc J* 1967; 97:1354-1357.
42. Majoros M, Parkhill EM, Devine K. Papilloma of the larynx in children: a clinicopathologic study. *Am J Surg* 1964; 108:470-475.
43. Singer DB, Greenberg SD, Harrison GM. Papillomatosis of the lung. *Am Rev Respir Dis* 1966; 94:777-783.
44. Kaufman G, Klopstock R. Papillomatosis of the respiratory tract. *Am Rev Respir Dis* 1963; 88:839-846.
45. Kirchner JA. Papilloma of the larynx with extensive lung involvement. *Laryngoscope* 1951; 61:1022-1029.
46. Kramer SS, Wehunt WD, Stocker JT, et al. Pulmonary manifestations of juvenile laryngotracheal papillomatosis. *AJR* 1985; 144:687-694.

47. Kawanami T, Bowen A. Juvenile laryngeal papillomatosis with pulmonary parenchymal spread. Case report and review of the literature. *Pediatr Radiol* 1985; 15:102-104.
48. Kerley SW, Buchon-Zalles C, Moran J, et al. Chronic cavitory respiratory papillomatosis. *Arch Pathol Lab Med* 1989; 13:1166-1169.
49. Kashima H, Mounts P, Leventhal B, et al. Sites of predilection in recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol* 1993; 102:580-583.
50. Pou AM, Rimell FL, Jordan JA, et al. Adult respiratory tract papillomatosis: Human papillomavirus type and viral coinfections are predictors of prognosis. *Ann Otol Rhinol Laryngol* 1995; 104:758-762.
51. Majoros M, Devine KD, Parkhill EM. Malignant transformation of benign laryngeal papillomas in children after radiation therapy. *Surg Clin North Am* 1963; 43: 1049-1061.
52. Quick CA, Foucar E, Dehner LP. Frequency and significance of epithelial atypia in laryngeal papillomatosis. *Laryngoscope* 1979; 89:550-560.
53. Stern Y, Hurtubise PE, Cotton RT. Significance of DNA ploidy and cell proliferation in juvenile respiratory papillomatosis. *Ann Otol Rhinol Laryngol* 1998; 107: 815-819.
54. Rady PL, Schnadig VJ, Weiss RL, et al. Malignant transformation of recurrent respiratory papillomatosis associated with integrated human papillomavirus type 11 DNA and mutation of p53. *Laryngoscope* 1998; 108:735-740.
55. Stern Y, Heffelfinger SC, Walner DL, et al. Expression of Ki-67, tumor suppressor genes, growth factor, and growth factor receptor in juvenile respiratory papillomatosis: Ki-67 and p53 as predictors of aggressive behavior. *Otolaryngol Head Neck Surg* 2000; 122:378-386.
56. Rabah R, Sakr W, Thomas R, et al. Human papillomavirus type, proliferative activity, and p53. Potential markers of aggressive papillomatosis. *Arch Pathol Lab Med* 2000; 124:721-724.
57. Go L, Schwartz MR, Donovan DT. Molecular transformation of recurrent respiratory papillomatosis: Viral typing and p53 overexpression. *Ann Otol Rhinol Laryngol* 2003; 112:298-302.
58. Lele SM, Pou Am, Ventura K, et al. Molecular events in the progression of recurrent respiratory papillomatosis to carcinoma. *Arch Pathol Lab Med* 2002; 126:1184-1188.
59. Xu H, Lu Dw, El-Mofty SK, et al. Metachronous squamous cell carcinoma evolving from independent oropharyngeal and pulmonary squamous papillomas: Association with human papillomavirus 11 and lack of aberrant p53, Rb and p16 protein expression. *Hum Pathol* 2004; 35:1419-1422.
60. Bonagura Vr, Hatam L, DeVoti J, et al. Recurrent respiratory papillomatosis: Altered CD8 T-cell subsets and TH 1/TH 2 cytokine imbalance. *Clin Immunol* 1999; 93: 302-311.
61. Gelder CM, Williams OM, Hart KW, et al. HLA class II polymorphisms and susceptibility to recurrent respiratory papillomatosis. *J Virol* 2003; 77:1927-1939.
62. Bonagura VR, Siegal FP, Abramson AL, et al. Enriched HLA-DQ3 phenotype and decreased class I major histocompatibility complex antigen expression in recurrent respiratory papillomatosis. *Clin Diagn Lab Immunol* 1994; 1:357-360.
63. Rahbar R, Vargas SO, Folkman J, et al. Role of vascular endothelial papillomatosis. *Ann Otol Rhinol Laryngol* 2005; 114:289-295.
64. Ruparella S, Munger ER, Nisenbaum R, et al. Predictors of remission in juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg* 2003; 129:1275-1278.
65. Szupnar J. Laryngeal papillomatosis. *Acta Otolaryngol* 1967; 63:74-86.
66. Bone RC, Feren AP, Nahum AM, et al. Laryngeal papillomatosis: immunologic and viral basis for therapy. *Laryngoscope* 1976; 86:341-348.
67. Stephens CB, Arnold GE, Butchko GM, et al. Autogenous vaccine therapy of juvenile laryngeal papillomatosis. *Laryngoscope* 1979; 89:1689-1696.
68. Cole RR, Myer CM III, Cotton RT. Tracheotomy in children with recurrent respiratory papillomatosis. *Head Neck* 1989; 11: 226-230.
69. Shapiro AM, Rimell FL, Shoemaker D, et al. Tracheotomy in children with juvenile onset recurrent respiratory papillomatosis: The Children's Hospital of Pittsburgh experience. *Ann Otol Rhinol Laryngol* 1996; 105:1-5.
70. Crockett DM, McCabe BF, Shive CJ. Complications of laser surgery for recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol* 1987; 96:639-644.
71. Steinberg BM, Topp WC, Schneider PS, et al. Laryngeal papillomavirus infection during clinical remission. *N Engl J Med* 1983; 308:1261-1264.
72. Pignatari S, Smith EM, Gray SD, et al. Detection of human papillomavirus in diseased and nondiseased sites of the respiratory tract in recurrent respiratory papillomatosis of patients by DNA hybridization. *Ann Otol Rhinol Laryngol* 1992; 101:408-412.
73. Smith EM, Pignatari SSN, Gray SD, et al. Human papillomavirus infection in papillomas and nondiseased respiratory sites of patients with recurrent respiratory papillomatosis using the polymerase chain reaction. *Arch Otolaryngol Head Neck Surg* 1993; 119:554-552.
74. Avidano MA, Singleton GT. Adjuvant drug strategies in the treatment of recurrent respiratory papillomatosis. *Otolaryngol Head Neck Surg* 1995; 112:197-202.
75. Schraff S, Derkay CS, Burke B, et al. American Society of Pediatric Otolaryngology members experience with recurrent respiratory papillomatosis and the use of adjuvant therapy. *Arch Otolaryngol Head Neck Surg* 2004; 130: 1039-1042.
76. Klos J. Clinical course of laryngeal papillomatosis in children. *Ann Otol Rhinol Laryngol* 1970; 79:1132-1138.
77. Solomon D, Smith RRL, Kashima HK, et al. Malignant transformation in non-irradiated recurrent respiratory papillomatosis. *Laryngoscope* 1985; 95:900-904.
78. Schnadig VJ, Clark WD, Clegg TJ, et al. Invasive papillomatosis and squamous carcinoma complicating juvenile laryngeal papillomatosis. *Arch Otolaryngol Head Neck Surg* 1986; 112:966-971.
79. Lim RY, Chang H-H. Malignant degeneration of a laryngeal papilloma. *Otolaryngol Head Neck Surg* 1987; 96:559-561.
80. Helmuth RA, Strate RW. Squamous carcinoma of the lung in nonirradiated, nonsmoking patient with juvenile laryngotracheal papillomatosis. *Am J Surg Pathol* 1987; 11:643-650.
81. Kashima H, Wu T-C, Mounts P, et al. Carcinoma ex-papilloma: histologic and virologic studies in whole-organ sections of the larynx. *Laryngoscope* 1988; 98: 619-624.
82. Guillou L, Sahli R, Chaubert P, et al. Squamous cell carcinoma of the lung in a non-smoking, nonirradiated patient with juvenile laryngotracheal papillomatosis. Evidence of human papillomavirus-11 DNA in both carcinoma and papillomas. *Am J Surg Pathol* 1991; 15:891-898.
83. Gaylis B, Hayden RE. Recurrent respiratory papillomatosis: progression to invasion and malignancy. *Am J Otolaryngol* 1991; 12:104-112.
84. Lindeberg H, Elbrond O. Malignant tumours in patients with a history of multiple laryngeal papillomas: the

significance of irradiation. *Clin Otolaryngol* 1991; 16: 149–151.

85. Siegel SE, Cohen SR, Isaacs H Jr., et al. Malignant transformation of tracheobronchial juvenile papillomatosis without prior irradiation. *Ann Otol Laryngol Rhinol* 1979; 88:192–197.
86. Doyle DJ, Henderson LA, LeJune FE Jr., et al. Changes in human papillomavirus typing of recurrent respiratory papillomatosis progressing to malignancy. *Arch Otolaryngol Head Neck Surg* 1994; 120:1273–1276.
87. Singh B, Ramsaroop R. Clinical features of malignant transformation in benign laryngeal papilloma. *J Laryngol Otol* 1994; 108:642–648.
88. Hasan S, Dutt SN, Kini U, et al. Laryngeal carcinoma ex-papilloma in a non-irradiated non-smoking patient: a clinical record and review of the literature. *J Laryngol Otol* 1995; 109:762–766.
89. Sakakura A, Yamamoto Y, Takasaki T, et al. Recurrent laryngeal papillomatosis developing into laryngeal carcinoma with human papilloma virus (HPV) type 18: a case report. *J Laryngol Otol* 1996; 110:75–77.
90. Moore CE, Wiatrak BJ, McClatchey KD, et al. High-risk human papillomavirus types and squamous cell carcinoma in patients with respiratory papillomas. *Otolaryngol Head Neck Surg* 1999; 120:698–705.
91. Cook JR, Hill A, Humphrey PA, et al. Squamous cell carcinoma arising in recurrent respiratory papillomatosis with pulmonary involvement: Emerging common pattern of clinical features and human papillomavirus serotype association. *Mod Pathol* 2000; 13:914–918.
92. Silver RD, Rimell FL, Adams GL, et al. Diagnosis and management of pulmonary metastasis from recurrent respiratory papillomatosis. *Otolaryngol Head Neck Surg* 2003; 129:622–629.
93. Crissman JD, Kessis T, Shah KV, et al. Squamous papillary neoplasia of the adult upper digestive tract. *Hum Pathol* 1988; 19:1387–1396.
94. Friedberg SA, Stagman R, Hass GM. Papillary lesions of the larynx in adults. A pathologic study. *Ann Otol Rhinol Laryngol* 1971; 80:683–692.
95. Johnson JT, Barnes EL, Justice W. Adult onset laryngeal papillomatosis. *Otolaryngol Head Neck Surg* 1981; 89:867–873.
96. Kimmich T, Kleinsasser O. Benign keratoma of the vocal cords. *Eur Arch Otorhinolaryngol* 1993; 250:143–149.
97. Barnes L, Peel RL. Papillary keratosis of larynx versus verrucous carcinoma of larynx. In: Barnes L, Peel RL, eds. *Head and Neck Pathology. A Text/Atlas of Differential Diagnosis*. New York: Igaku-Shoin, 1990:80–81.
98. Ferlito A, Recher G. Ackerman's tumor (verrucous carcinoma of the larynx). A clinicopathologic study of 77 cases. *Cancer* 1980; 46:1617–1630.
5. Eversole LR, Laipis PJ, Green TL. Human papillomavirus type-2 DNA in oral and labial verruca vulgaris. *J Cutan Pathol* 1987; 14:319–325.
6. Barnes L, Yunis EJ, Krebs FJ III, et al. Verruca vulgaris of the larynx. Demonstration of human papillomavirus types 6/11 by in situ hybridization. *Arch Pathol Lab Med* 1991; 115:895–899.
7. Jenson AB, Lancaster WD, Hartmann D-P, et al. Frequency and distribution of papillomavirus structural antigens in verrucae, multiple papillomas, and condylomata of the oral cavity. *Am J Pathol* 1982; 107:212–218.
8. Nash M, Lucente F, Srinivasan K, et al. Condylomatous lesions of the upper aerodigestive tract. *Laryngoscope* 1987; 97:1410–1416.
9. Nuovo GJ, O'Connell M, Blanco JS, et al. Correlation of histology and human papillomavirus DNA detection in condylomata acuminatum and condyloma-like vulvar lesions. *Am J Surg Pathol* 1989; 13:700–706.
10. Ferlito A, Recher G. Ackerman's tumor (verrucous carcinoma) of the larynx. A clinicopathologic study of 77 cases. *Cancer* 1980; 46:1617–1630.

VIII. VERRUCA VULGARIS

1. Wysocki GP, Hardie J. Ultrastructural studies of intraoral verruca vulgaris. *Oral Surg Oral Med Oral Pathol* 1979; 47:58–62.
2. Fechner RE, Mills SE. Verruca vulgaris of the larynx. A distinctive lesion of probable viral origin confused with verrucous carcinoma. *Am J Surg Pathol* 1982; 6:357–362.
3. Adler-Storthez K, Newland JR, Tessin BA, et al. Identification of human papillomavirus types in oral verruca vulgaris. *J Oral Pathol* 1986; 15:230–233.
4. Green TL, Eversole LR, Leider AS. Oral and labial verruca vulgaris: clinical, histologic and immunohistochemical evaluation. *Oral Surg Oral Med Oral Pathol* 1986; 62:410–416.

IX. BENIGN NONEPITHELIAL TUMORS OF THE LARYNX

1. New GB, Erich JB. Benign tumors of the larynx. A study of seven hundred and twenty- two cases. *Arch Otolaryngol* 1938; 28:841–910.
2. Holinger PH, Johnston KC. Benign tumors of the larynx. *Ann Otol Rhinol Laryngol* 1951; 60:496–509.
3. Myers JN, Myers EN, Barnes EL. Benign neoplasms of the larynx. In: Fried, ed. *The Larynx. A Multidisciplinary Approach*. 2nd ed. St. Louis: Mosby, 1996:443–459.
4. Ferguson CF, Flake CG. Subglottic hemangioma as a cause of respiratory obstruction in infants. *Ann Otol Rhinol Laryngol* 1961; 70:1095–1112.
5. Holinger PH, Brown WT. Congenital webs, cysts, laryngoceles and other anomalies of the larynx. *Ann Otol Rhinol Laryngol* 1967; 76:744–752.
6. Shikhani AH, Jones MM, Marsh BR, et al. Infantile subglottic hemangiomas. An update. *Ann Otol Rhinol Laryngol* 1986; 95:336–347.
7. Bitar MA, Moukarbel RV, Zalzal GH. Management of congenital subglottic hemangioma: Trends and success over the past 14 years. *Otolaryngol Head Neck Surg* 2005; 132:226–231.
8. Woolley AL, Lusk RP. Multiple vascular lesions of an infant's airway. *Otolaryngol Head Neck Surg* 1994; 111:305–308.
9. Brodsky L, Yoshpe N, Ruben RJ. Clinical-pathological correlates of congenital subglottic hemangiomas. *Ann Otol Rhinol Laryngol* 1983; 92 (suppl 105):4–18.
10. Pransky SM, Canto C. Management of subglottic hemangioma. *Curr Opin Otolaryngol Head Neck Surg* 2004; 12:509–512.
11. Ferguson GB. Hemangioma of the adult and of the infant larynx. A review of the literature and report of two cases. *Arch Otolaryngol* 1944; 40:189–195.
12. Mugliston TAH, Sangwan S. Persistent cavernous hemangioma of the larynx—a pregnancy problem. *J Laryngol Otol* 1985; 99:1309–1311.
13. Cummings CW, Montgomery WW, Balogh K Jr. Neurogenic tumors of the larynx. *Laryngoscope* 1969; 78:79–95.
14. Schaeffer BT, Som PM, Biller HF, et al. Schwannomas of the larynx: a review and computed tomographic scan analysis. *Head Neck Surg* 1986; 8:469–472.
15. Barnes L, Ferlito A. Soft tissue tumors. In: Ferlito A, ed. *Neoplasms of the Larynx*. Edinburgh: Churchill Livingstone, 1993:265–304.

16. Supance JS, Quenelle DJ, Crissman J. Endolaryngeal neurofibromas. *Otolaryngol Head Neck Surg* 1980; 88:74–78.
17. Takumida M, Taira T, Suzuki M, et al. Neurilemoma of the larynx. *J Laryngol Otol* 1986; 100:847–850.
18. White AK, Smith RJH, Bigler CR, et al. Head and neck manifestations of neurofibromatosis. *Laryngoscope* 1986; 96:732–737.
19. Fukuda I, Ogasawara H, Kumoi T, et al. Subglottic neurofibroma in a child. *Int J Pediatr Otorhinolaryngol* 1987; 14:161–170.
20. Willcox TO Jr., Rosenberg SI, Handler SD. Laryngeal involvement in neurofibromatosis. *ENT J* 1993; 72:811–815.
21. Ingels K, Vermeersch H, Verhoye C, et al. Schwannoma of the larynx: a case report. *J Laryngol Otol* 1996; 110: 294–296.
22. Masip MJ, Esteban E, Alberto C, et al. Laryngeal involvement in pediatric neurofibromatosis: a case report and review of the literature. *Pediatr Radiol* 1996; 26:488–492.
23. Zbaren P, Markwalder R. Schwannoma of the true vocal cord. *Otolaryngol Head Neck Surg* 1999; 121:837–839.
24. Nakahira M, Nakatani H, Sawada S, et al. Neurofibroma of the larynx in neurofibromatosis. Preoperative computed tomography and magnetic resonance imaging. *Arch Otolaryngol Head Neck Surg* 2001; 127:325–328.
25. Rosen FS, Pou AM, Quinn FB Jr. Obstructive supraglottic schwannoma: A case report and review of the literature. *Laryngoscope* 2002; 112:997–1002.
26. Yucel EA, Guldiken Y, Ozdemir M, et al. Plexiform neurofibroma of the larynx in a child. *J Laryngol Otol* 2002; 116:49–51.
27. Rahbar R, Litrovnik BG, Vargas SO, et al. The biology and management of laryngeal neurofibroma. *Arch Otolaryngol Head Neck Surg* 2004; 130:1400–1406.
28. Sidman J, Wood RE, Poole M, et al. Management of plexiform neurofibroma of the larynx. *Ann Otol Rhinol Laryngol* 1987; 96:53–55.
29. Lippert BM, Eggers S, Schluter E, et al. Lipoma of the larynx. Report of 2 cases and review of the literature. *Otolaryngol Pol* 2002; 56:669–674.
30. Zakrzewski A. Subglottic lipoma of the larynx (case report and literature review). *J Laryngol Otol* 1965; 79:1039–1048.
31. Wenig BM. Lipomas of the larynx and hypopharynx: a review of the literature with the addition of three new cases. *J Laryngol Otol* 1995; 109:353–357.
32. Yoskovitch A, Cambronero E, Said S, et al. Giant lipoma of the larynx: A case report and literature review. *ENT J* 1999; 78:122–125.
33. Jungehulsing M, Fischbach R, Pototschnig C, et al. Rare benign tumors. Laryngeal and hypopharyngeal lipomata. *Ann Otol Rhinol Laryngol* 2000; 109:301–305.
34. Moretti JA, Miller D. Laryngeal involvement in benign symmetric lipomatosis. *Arch Otolaryngol* 1973; 97:495–496.
35. Ortiz CL, Weber AL. Laryngeal lipoma. *Ann Otol Rhinol Laryngol* 1991; 100:783–784.
36. Dinsdale RC, Manning SC, Brooks DJ, et al. Myxoid laryngeal lipoma in a juvenile. *Otolaryngol Head Neck Surg* 1990; 103:653–657.
37. Nonako S, Enomoto K, Kawabori S, et al. Spindle cell lipoma within the larynx: a case report with correlated light and electron microscopy. *ORL* 1993; 55:147–149.
38. Chen KTK, Weinberg RA. Intramuscular lipoma of the larynx. *Am J Otolaryngol* 1984; 5:71–72.
39. Franceschini S, Segnini G, Berrettini S, et al. Hibernoma of the larynx. Review of the literature and a new case. *Acta Otorhinolaryngol Belg* 1993; 47:51–53.
40. Wenig BM, Weiss SW, Gnepp DR. Laryngeal and hypopharyngeal liposarcomas: a clinicopathologic study of 10 cases with a comparison of soft tissue counterparts. 1990; 14:131–141.
41. Farman AG. Benign smooth muscle tumors. *S Afr Med J* 1975; 49:1333–1340.
42. Harris PF, Ward PH. Leiomyoma of the larynx and trachea: case reports. *South Med J* 1967; 60:1223–1227.
43. Karma P, Rasanen O. Laryngeal leiomyoma. *J Laryngol Otol* 1978; 92:411–415.
44. Kleinsasser O, Glanz H. Myogenic tumors of the larynx. *Arch Otorhinolaryngol* 1979; 225:107–119.
45. Kaya S, Saydam L, Ruacan S. Laryngeal leiomyoma. *Int J Pediatr Otorhinolaryngol* 1990; 19:285–288.
46. McKiernan DC, Watters GWR. Smooth muscle tumours of the larynx. *J Laryngol Otol* 1995; 109:77–79.
47. Shibata K, Komune S. Laryngeal angiomyoma (vascular leiomyoma): clinicopathologic findings. *Laryngoscope* 1980; 90:1880–1886.
48. Nuutinen J, Syrjanen K. Angioleiomyoma of the larynx. Report of a case and review of the literature. *Laryngoscope* 1983; 93:941–943.
49. Hirakawa K, Harada Y, Tatsukawa T, et al. A case of vascular leiomyoma of the larynx. *J Laryngol Otol* 1994; 108:593–595.
50. Mori H, Kumoi T, Hashimoto M, et al. Leiomyoblastoma of the larynx: report of a case. *Head Neck* 1992; 14:148–152.
51. Hellquist HB, Hellqvist H, Vejens L, et al. Epithelioid leiomyoma of the larynx. *Histopathology* 1994; 24: 155–159.

X. KERATOSIS WITH AND WITHOUT DYSPLASIA

1. McGavran MH, Bauer WC, Ogura JH. Isolated laryngeal keratosis. Its relation to carcinoma of the larynx based on a clinicopathologic study of 87 consecutive cases with long-term follow-up. *Laryngoscope* 1960; 70:932–951.
2. Hellquist H, Lundgren J, Olofsson J. Hyperplasia, keratosis, dysplasia and carcinoma in situ of the vocal cords—a follow-up study. *Clin Otolaryngol* 1982; 7:11–27.
3. Sillamniku B, Bauer W, Painter C, et al. The transformation of laryngeal keratosis into invasive carcinoma. *Am J Otolaryngol* 1989; 10:42–54.
4. Gallo A, de Vincentiis M, Rocca CD, et al. Evolution of precancerous laryngeal lesions: A clinicopathologic study with long-term follow-up on 259 patients. *Head Neck* 2001; 23:42–47.
5. Ricci G, Molini E, Faralli M, et al. Retrospective study on precancerous laryngeal lesions: long-term follow-up. *Acta Otorhinolaryngol Ital* 2003; 23:362–367.
6. Henry RC. The transformation of laryngeal leukoplakia to cancer. *J Laryngol Otol* 1979; 93:447–459.
7. Lederman M. Keratosis of the larynx. *J Laryngol Otol* 1963; 77:651–659.
8. Bouquot JE, Gnepp DR. Laryngeal precancer: a review of the literature, commentary, and comparison with oral leukoplakia. *Head Neck* 1991; 13:488–497.
9. Norris CM, Peale AR. Keratosis of the larynx. *J Laryngol Otol* 1963; 77:635–647.
10. Putney FJ, O'Keefe JJ. The clinical significance of keratosis of the larynx as a premalignant lesion. *Ann Otol Rhinol Laryngol* 1953; 62:348–357.
11. Gabriel CE, Jones DG. Hyperkeratosis of the larynx. *J Laryngol Otol* 1973; 87:129–134.
12. Crissman JD. Laryngeal keratosis and subsequent carcinoma. *Head Neck Surg* 1979; 1:386–391.
13. Gillis TM, Ineze J, Strong MS, et al. Natural history and management of keratosis, atypia, carcinoma in situ, and microinvasive carcinoma of the larynx. *Am J Surg* 1983; 146:512–516.

14. Kalter PO, Lubsen H, Delemarre JFM, et al. Squamous cell hyperplasia of the larynx (a clinical follow-up study). *J Laryngol Otol* 1987; 101:579–588.
 15. Hojslet P-E, Nielson VM, Palvio D. Premalignant lesions of the larynx. A follow-up study. *Acta Otolaryngol (Stockh)* 1989; 107:150–155.
 16. Cuchi A, Bombi JA, Avellaneda R, et al. Precancerous lesions of the larynx: clinical and pathologic correlations and prognostic aspects. *Head Neck* 1994; 16:545–549.
 17. Blackwell KE, Fu Y-S, Calcaterra TC. Laryngeal dysplasia. A clinicopathologic study. *Cancer* 1995; 75:457–463.
 18. Jeannon J-P, Soames JV, Aston V, et al. Molecular markers in dysplasia of the larynx: expression of cyclin-dependent kinase inhibitors p21, p27 and p53 tumor suppressor gene in predicting cancer risk. *Clin Otolaryngol* 2004; 29: 698–704.
 19. Bocking A, Aufferman W, Vogel H, et al. Diagnosis and grading of malignancy in squamous epithelial lesions of the larynx with DNA cytophotometry. *Cancer* 1985; 56:1600–1604.
 20. Olofsson J, Franzen G, Lundgren J. Hypertetraploid cells in vocal cord epithelia. *Clin Otolaryngol* 1986; 11:345–351.
 21. Munck-Wickland E, Kulenstierna R, Lindholm J, et al. Image cytometry DNA analysis of dysplastic squamous epithelial lesions in the larynx. *Anticancer Res* 1991; 11:597–600.
 22. Crissman JD, Zarbo RJ. Quantitation of DNA ploidy in squamous intraepithelial neoplasia of the laryngeal glottis. *Arch Otolaryngol Head Neck Surg* 1991; 117:182–188.
- XI. CARCINOMA IN SITU**
1. Kelinsasser O. Mikrolarynoskopie und Endolarungeale. Mikrochirurgie. Technik und Typische Befunde. Stuttgart: Schattauer-Verlag, 1968.
 2. Altman F, Ginsberg I, Stout AP. Intraepithelial cancer (carcinoma in situ) of the larynx. *Arch Otolaryngol* 1952; 56:121–133.
 3. Bauer WC, McGravran MH. Carcinoma in situ and evaluation of epithelial changes in laryngopharyngeal biopsies. *JAMA* 1972; 221:72–75.
 4. DeSanto LW. Selection of treatment for in situ and early invasive carcinoma of the glottis. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1976:146–150.
 5. Hawkins NV. Panel discussion on glottic tumors. VIII. The treatment of glottic carcinoma: an analysis of 800 cases. *Laryngoscope* 1975; 85:1485–1493.
 6. Miller AH. Carcinoma in situ of the larynx—clinical appearance and treatment. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1976:161–166.
 7. Elman AJ, Goodman M, Wang CC, et al. In situ carcinoma of the vocal cords. *Cancer* 1979; 43:2422–2428.
 8. Maran AGD, MacKenzie IJ, Stanley RE. Carcinoma in situ of the larynx. *Head Neck Surg* 1984; 7:28–31.
 9. McGuirt WF, Browne JD. Management decisions in laryngeal carcinoma in situ. *Laryngoscope* 1991; 101:125–129.
 10. Rothfield RE, Myers EN, Johnson JT. Carcinoma in situ and microinvasive squamous cell carcinoma of the vocal cords. *Ann Otol Rhinol Laryngol* 1991; 100:793–796.
 11. Hintz BL, Kagan AR, Nussbaum H, et al. A “watchful waiting” policy for in situ carcinoma of the vocal cords. *Arch Otolaryngol* 1981; 107:746–751.
 12. Myssiorek D, Vambutas, Abramson AL. Carcinoma in situ of the glottic larynx. *Laryngoscope* 1994; 104:463–467.
 13. Brooks JP, Morgan DW, Glaholm J. Twelve cases of glottic carcinoma in situ treated by radiotherapy: an observation on clinical course versus response. *J Laryngol Otol* 1993; 107:1014–1016.
 14. Murty GE, Diver JP, Bradley PJ. Carcinoma in situ of the glottis: Radiotherapy or excision biopsy? *Ann Otol Rhinol Laryngol* 1993; 102:592–595.
 15. Small W Jr., Mittal BB, Brand WN, et al. Role of radiation therapy in the management of carcinoma in situ of the larynx. *Laryngoscope* 1993; 103:663–667.
 16. Le Q-T, Takamiya R, Shu H-K, et al. Treatment results of carcinoma in situ of the glottis. An analysis of 82 cases. *Arch Otolaryngol Head Neck Surg* 2000; 126:1305–1312.
 17. Spayne JA, Warde P, O’Sullivan B, et al. Carcinoma-in-situ of the glottic larynx: Results of treatment with radiation therapy. *Int J Radiat Oncol Biol Phys* 2001; 49: 1235–1238.
 18. Garcia-Serra A, Hinerman RW, Amdur RJ, et al. Radiotherapy for carcinoma in situ of the true vocal cords. *Head Neck* 2002; 24:390–394.
 19. Sanz-Ortega J, Valor C, Saez MC, et al. 3p21, 5q21, 9p21, and 17p13 allelic deletions accumulate in the dysplastic spectrum of laryngeal carcinogenesis and precede malignant transformation. *Histol Histopathol* 2003; 18: 1053–1057.
 20. Nadal A, Campo E, Pinto J, et al. p53 expression in normal, dysplastic, and neoplastic laryngeal epithelium. Absence of correlation with prognostic factors. *J Pathol* 1995; 17:181–188.
 21. Gallo O, Santucci M, Franchi A. Cumulative prognostic value of p16/CDKN2 and p53 oncoprotein expression in premalignant laryngeal lesions. *J Natl Cancer Inst* 1997; 89:1161–1163.
 22. Gallo O, Franchi A, Chiarelli I, et al. Potential biomarkers in predicting progression of epithelial hyperplastic lesions of the larynx. *Acta Otolaryngol (Stockh)* 1997; Suppl 527:30–38.
 23. Jin Y-T, Kayser S, Kemp BL, et al. The prognostic significance of the biomarkers p21, p53, and bcl-2 in laryngeal squamous cell carcinomas. *Cancer* 1998; 82:2159–2165.
 24. Narayana A, Vaughan ATM, Gunaratne S, et al. Is p53 an independent prognostic factor in patients with laryngeal carcinoma? *Cancer* 1998; 82:286–291.
 25. Jeannon J-P, Soames JV, Aston V, et al. Molecular markers in dysplasia of the larynx: expression of cyclin-dependent kinase inhibitors p21, p27, and p53 tumor suppressor gene in predicting cancer risk. *Clin Otolaryngol* 2004; 29:698–704.
 26. Hussein MR. Alterations of p53 and BCL-2 protein expression in the laryngeal intraepithelial neoplasia. *Cancer Biol Ther* 2005; 4:213–217.
 27. Kleinsasser O. Cancer of the larynx, a study of development and early growth. *J Otolaryngol Soc Aust* 1968; 2: 8–12.
 28. Miller AH, Fisher HR. Clues to the life history of carcinoma in situ of the larynx. *Laryngoscope* 1971; 81:1475–1480.
 29. Holinger PH, Schild JA. Carcinoma in situ of the larynx. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1974:143–144.
 30. Som ML. Surgery in premalignant lesions. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1974:145.
 31. Pene F, Fletcher GH. Results in irradiation of the in situ carcinomas of the vocal cords. *Cancer* 1976; 37:2586–2590.
 32. Hellquist H, Lundgren J, Olofsson J. Hyperplasia, keratosis, dysplasia, and carcinoma in situ of the vocal cords—a follow-up study. *Clin Otolaryngol* 1982; 7:11–27.
 33. Gillis TM, Ineze J, Strong MS, et al. Natural history and management of keratosis, atypia, carcinoma in situ, and microinvasive carcinoma. *Am J Surg* 1983; 146:512–515.

34. Kalter PO, Lubsen H, Delemarre JFM, et al. Squamous cell hyperplasia of the larynx (a clinical follow-up study). *J Laryngol Otol* 1987; 101:579–588.
35. Shvero J, Hadar T, Segal K, et al. Carcinoma in situ of the vocal cords: a retrospective study. *Clin Otolaryngol* 1988; 13:235–237.
36. Crissman JD, Zarbo RJ, Drozdowicz S, et al. Carcinoma in situ and microinvasive squamous carcinoma of the laryngeal glottis. *Arch Otolaryngol Head Neck Surg* 1988; 114:299–307.
37. Stenersen T. Chr., Hoel PS, Boysen M. Carcinoma in situ of the larynx: an evaluation of its natural course. *Clin Otolaryngol* 1991; 16:358–363.
38. Small W Jr., Mittal BB, Brand WN, et al. Role of radiation therapy in management of carcinoma in situ of the larynx. *Laryngoscope* 1993; 103:663–667.
39. Blackwell KE, Calcaterra TC, Fu Y-S. Laryngeal dysplasia: Epidemiology and treatment outcome. *Ann Otol Rhinol Laryngol* 1995; 104:596–602.
40. Nasser VH, Bridger GP. Topography of the laryngeal mucous glands. *Arch Otolaryngol* 1971; 94:490–498.
41. Bridger GP, Nasser VH. Carcinoma in situ involving the laryngeal mucous glands. *Arch Otolaryngol* 1971; 94:389–400.
42. Freeland AP, van Nostrand AWP. The applied anatomy of the anterior commissure and subglottis. *Can J Otolaryngol* 1975; 4:644–658.
2. Sulfaro S, Volpe R, Barzan L, et al. Superficial extending carcinoma of the larynx. *Laryngoscope* 1988; 98: 1127–1132.
3. Carbone A, Volpe R, Barzan L. Superficial extending carcinoma (SEC) of the larynx and hypopharynx. *Pathol Res Pract* 1992; 188:729–735.
4. Bogomoletz WV. Early gastric cancer. *Am J Surg Pathol* 1984; 8:381–391.
5. Bogomoletz WV, Molas G, Gayet B, et al. Superficial squamous cell carcinoma of the esophagus. A report of 76 cases and review of the literature. *Am J Surg Pathol* 1989; 13:535–546.
6. Rubio CA, Liu F-S, Zhao H-Z. Histological classification of intraepithelial neoplasias and microinvasive squamous carcinoma of the esophagus. *Am J Surg Pathol* 1989; 13:685–690.
7. Nagawa H, Kaizaki S, Seto Y, et al. The relationship of macroscopic shape of superficial esophageal carcinoma to depth of invasion and regional lymph node metastasis. *Cancer* 1995; 75:1061–1064.
8. Ferlito A. The natural history of early vocal cord cancer. *Acta Otolaryngol* 1995; 115:345–347.
9. Ferlito A, Carbone A, DeSanto LW, et al. “Early” cancer of the larynx: the concept as defined by clinicians, pathologists, and biologists. *Ann Otol Rhinol Laryngol* 1996; 105:245–250.
10. DeSanto LW, Olsen KD. Early glottic carcinoma. *Am J Otolaryngol* 1994; 15:242–249.
11. Mendenhall WM, Parsons JT, Stringer SP, et al. Management of T1S, T1 and T2 squamous cell carcinoma of the glottic larynx. *Am J Otolaryngol* 1994; 15:250–257.
12. Morris MR, Canonico D, Blank C. A critical review of radiotherapy in the management of T1 glottic carcinoma. *Am J Otolaryngol* 1994; 15:276–280.
13. Shvero J, Hadar T, Segal K, et al. Early glottic carcinoma involving the anterior commissure. *Clin Otolaryngol* 1994; 19:105–108.
14. Mahieu HF, Patel P, Annyas AA, et al. Carbon dioxide laser vaporization in early glottic carcinoma. *Arch Otolaryngol Head Neck Surg* 1994; 120:383–387.
15. Thomas JV, Olsen KD, Neel HB III, et al. Recurrences after endoscopic management of early (T1) glottic carcinoma. *Laryngoscope* 1994; 104:1099–1104.

XII. MICROINVASIVE (SUPERFICIAL) CARCINOMA OF THE LARYNX

1. Miller AH. Carcinoma in situ of the larynx—clinical appearance and treatment. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1976:161–166.
2. Freidmann I. Precancerous lesions of the larynx. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1976:122–126.
3. Padovan IF. Premalignant laryngeal lesions—a laryngologist’s viewpoint. In: Alberti PW, Bryce DP, eds. Centennial Conference on Laryngeal Carcinoma. New York: Appleton-Century-Crofts, 1976:137–139.
4. Crissman JD, Zarbo RJ, Drozdowicz S, et al. Carcinoma in situ and microinvasive squamous carcinoma of the laryngeal glottis. *Arch Otolaryngol Head Neck Surg* 1988; 114:299–307.
5. Myers EN, Wagner RL, Johnson JT. Microlaryngoscopic surgery for T1 glottic lesions: A cost-effective option. *Ann Otol Rhinol Laryngol* 1994; 103:28–30.
6. Nguyen C, Naghibzadeh B, Black MJ, et al. Glottic microinvasive carcinoma: Is it different from carcinoma in situ? *J Otolaryngol* 1996; 25:223–226.
7. McGuirt WF, Browne JD. Management decisions in laryngeal carcinoma in situ. *Laryngoscope* 1991; 101:125–129.
8. Rotfield RE, Myers EN, Johnson JT. Carcinoma in situ and microinvasive squamous cell carcinoma of the vocal cords. *Ann Otol Rhinol Laryngol* 1991; 100:793–796.
9. Stutsman AC, McGavran MH. Ultraconservative management of superficially invasive epidermoid carcinoma of the true vocal cord. *Ann Otol Rhinol Laryngol* 1971; 80: 507–512.

XIII. SUPERFICIAL EXTENDING CARCINOMA

1. Carbone A, Micheau C, Bosq J, et al. Superficial extending carcinoma of the hypopharynx: report of 26 cases of an underestimated carcinoma. *Laryngoscope* 1983; 93:1600–1606.

XIV. SQUAMOUS CELL CARCINOMA OF THE LARYNX

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA* 2006; 56:106–130.
2. Hodge KM, Flynn MB, Drury T. Squamous cell carcinoma of the upper aerodigestive tract in nonusers of tobacco. *Cancer* 1985; 55:1232–1235.
3. Robin PE, Reid A, Powell DJ, et al. The incidence of cancer of the larynx. *Clin Otolaryngol* 1991; 16:198–201.
4. Decker J, Goldstein JC. Risk factors in head and neck cancer. *N Engl J Med* 1982; 306:1151–1156.
5. Morrison MD. Is chronic gastroesophageal reflux a causative factor in glottic carcinoma? *Otolaryngol Head Neck Surg* 1988; 9:370–373.
6. Parnes SM. Asbestos and cancer of the larynx: is there a relationship? *Laryngoscope* 1990; 100:254–261.
7. Cauvin JM, Guenel P, Luce D, et al. Occupational exposure and head and neck carcinoma. *Clin Otolaryngol* 1990; 15:439–445.
8. Hoshikawa T, Nakajima T, Uhara H, et al. Detection of human papillomavirus DNA in laryngeal squamous cell carcinomas by polymerase chain reaction. *Laryngoscope* 1990; 100:647–650.

9. Maier H, DeVries N, Snow GB. Occupational factors in the etiology of head and neck cancer. *Clin Otolaryngol* 1991; 16:406-412.
10. Muscat JE, Wynder EL. Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. *Cancer* 1992; 69:2244-2251.
11. Waterhouse JAH. Epidemiology. In: Ferlito A, ed. *Neoplasms of the Larynx*. Edinburgh: Churchill Livingstone, 1993:49-64.
12. Wake M. The Urban/rural divide in head and neck cancer—the effect of atmospheric pollution. *Clin Otolaryngol* 1993; 18:298-302.
13. Lawson W, Biller HF, Suen JY. Cancer of the larynx. In: Meyers EN, Suen JY, eds. *Cancer of the Head and Neck*. 2nd ed. New York: Churchill Livingstone, 1989:533-591.
14. DeRienzo DP, Greensburgh SD, Fraire AE. Carcinoma of the larynx. Changing incidence in women. *Arch Otolaryngol Head Neck Surg* 1991; 117:681-684.
15. Hast MH. Applied embryology of the larynx. In: Alberti PWW, Bryce DP, eds. *Centennial Conference on Laryngeal Carcinoma*. New York: Appleton-Century-Crofts, 1976:6-9.
16. Pressman JJ. Submucosal compartmentalization of the larynx. *Ann Otol Rhinol Laryngol* 1956; 65:766-771.
17. Pressman JJ, Simon MB, Monell C. Anatomical studies related to the dissemination of cancer of the larynx. *Trans Am Acad Ophthalmol Otolaryngol* 1960; 64:628-638.
18. Tucker GF Jr., Smith HR. A histological demonstration of the development of laryngeal connective tissue compartments. *Trans Am Acad Ophthalmol Otolaryngol* 1962; 66:308-318.
19. Kirchner JA, Carter D. Intralaryngeal barriers to the spread of cancer. *Acta Otolaryngol* 1987; 103:503-513.
20. Broyles EN. The anterior commissure tendon. *Ann Otol Rhinol Laryngol* 1943; 52:342-345.
21. Olofsson J, Williams GT, Rider WD, et al. Anterior Commissure carcinoma. Primary treatment with radiotherapy in 57 patients. *Arch Otolaryngol* 1972; 95:230-239.
22. Clerf LH. The pre-epiglottic space. Its relation to carcinoma of the epiglottis. *Arch Otolaryngol* 1944; 40:177-179.
23. Dayal VS, Bahri H, Stone PC. Pre-epiglottic space. An anatomic study. *Arch Otolaryngol* 1972; 95:130-133.
24. Maquire A, Dayal VS. Supraglottic anatomy the pre- or peri-epiglottic space? In: Alberti PW, Bryce DP, eds. *Centennial Conference on Laryngeal Cancer*. New York: Appleton-Century-Crofts, 1976:26-33.
25. Lam KH, Wong J. The preepiglottic and paraglottic spaces in relation to spread of carcinoma of the larynx. *Am J Otolaryngol* 1983; 4:81-91.
26. Gregor RT. The preepiglottic space revisited: is it significant? *Am J Otolaryngol* 1990; 11:161-164.
27. Zeitels SM, Vaughan CW. Preepiglottic space invasion in "early" epiglottic cancer. *Ann Otol Rhinol Laryngol* 1991; 100:789-792.
28. Sato K, Kurita S, Hirano M. Location of the preepiglottic space and its relationship to the paraglottic space. *Ann Otol Rhinol Laryngol* 1993; 102:930-934.
29. Tucker GF Jr. The anatomy of laryngeal cancer. In: Alberti PW, Bryce DP, eds. *Centennial Conference on Laryngeal Cancer*. New York: Appleton-Century-Crofts, 1976:11-24.
30. Green FL, Page DL, Fleming ID, et al, eds. *American Joint Committee on Cancer. Manual for Staging of Cancer*. 6th ed. New York: Springer, 2002:47-57.
31. Rowley NJ, Boyles R. Supraglottic carcinoma: a 10 year review at the University Hospital. *Laryngoscope* 1972; 82:1264-1272.
32. Smith RR, Caulk R, Frazell E. Revision of the clinical staging system for cancer of the larynx. *Cancer* 1973; 31:72-80.
33. Coates HL, DeSanto LW, Devine KD, et al. Carcinoma of the supraglottic larynx. A review of 221 cases. *Arch Otolaryngol* 1976; 102:686-689.
34. Bocca E, Pignataro O, Mosciaro O. Supraglottic surgery of the larynx. *Ann Otol Rhinol Laryngol* 1968; 77:1005-1026.
35. Olofsson J. Growth and spread of laryngeal carcinoma. In: Alberti PW, Bryce DP, eds. *Centennial Conference on Laryngeal Carcinoma*. New York: Appleton-Century-Crofts, 1976:40-53.
36. McDonald TJ, DeSanto LW, Weiland LH. Supraglottic larynx and its pathology as studied by whole laryngeal sections. *Laryngoscope* 1976; 86:635-648.
37. Lutz CK, Johnson JT, Wagner RL, et al. Supraglottic carcinoma: patterns of recurrence. *Ann Otol Rhinol Laryngol* 1990; 99:12-17.
38. Sessions DG. Surgical pathology of cancer of the larynx and hypopharynx. *Laryngoscope* 1976; 86:814-839.
39. Ogura JH. Surgical pathology of cancer of the larynx. *Laryngoscope* 1955; 65:867-926.
40. Bocca E. Supraglottic cancer. *Laryngoscope* 1975; 85:1318-1326.
41. Kirchner JA. What have whole organ sections contributed to the treatment of laryngeal cancer. *Ann Otol Rhinol Laryngol* 1989; 98:661-667.
42. Bocca E. Surgical management of supraglottic cancer and its lymph node metastases in a conservative perspective. *Ann Otol Rhinol Laryngol* 1991; 100:261-267.
43. Weinstein GS, Laccourreye O, Brasnu D, et al. Reconsidering a paradigm: The spread of supraglottic carcinoma of the glottis. *Laryngoscope* 1995; 105:1129-1133.
44. Kirchner JA, Som ML. Clinical and histological observations on supraglottic cancer. *Ann Otol Rhinol Laryngol* 1971; 80:638-645.
45. Shah JP, Tollefson HR. Epidermoid carcinoma of the supraglottic larynx. Role of neck dissection in initial surgical treatment. *Am J Surg* 1974; 128:494-499.
46. Ogura JH, Sessions DG, Spector GJ. Conservation surgery for epidermoid carcinoma of the supraglottic larynx. *Laryngoscope* 1974; 85:1808-1815.
47. Meyer-Breiting E, von Ilberg C. Spread and mode of metastases of supraglottic laryngeal carcinoma. *ORL* 1979; 41:288-300.
48. Burstein FD, Calcaterra TC. Supraglottic laryngectomy: series report and analysis of results. *Laryngoscope* 1985; 95:833-836.
49. Spaulding CA, Krochak RJ, Hahn SS, et al. Radiotherapeutic management of cancer of the supraglottis. *Cancer* 1986; 57:1292-1298.
50. Guerrier B, Balmigere G, Daures JP, et al. Cancer of the laryngeal vestibule. *Arch Otorhinolaryngol* 1989; 246:378-381.
51. DeSanto LW. Early supraglottic cancer. *Ann Otol Rhinol Laryngol* 1990; 99:593-597.
52. Lee NK, Goepfert H, Wendt CD. Supraglottic laryngectomy for intermediate-stage cancer: UT M.D. Anderson Cancer Center experience with combined therapy. *Laryngoscope* 1990; 100:831-836.
53. Zamora RL, Harvey JE, Sessions DG, et al. Clinical staging for primary malignancies of the supraglottic larynx. *Laryngoscope* 1993; 103:69-77.
54. de Guzman RB, Martorell MA, Basterra J, et al. Prognostic value of histopathological parameters in 51 supraglottic squamous cell carcinomas. *Laryngoscope* 1993; 103:538-540.
55. McGavran MH, Bauer WC, Ogura JH. The incidence of cervical lymph node metastases from epidermoid carcinoma of the larynx and their relationship to certain characteristics of the primary tumor. A study based on the clinical and pathological findings for 96 patients

- treated by primary en bloc laryngectomy and radical neck dissection. *Cancer* 1961; 14:55–66.
56. Fiend CR, Cole RM. Contralateral spread of head and neck cancer. *Am J Surg* 1969; 118:660–665.
57. Cocke EW Jr., Wang CC. Part I. Cancer of the larynx: selecting optimal treatment. *CA* 1976; 26:194–200.
58. Razack MS, Silapasvang S, Sako K, et al. Significance of site and nodal metastases in squamous cell carcinoma of the epiglottis. *Am J Surg* 1978; 136:520–524.
59. Marks JE, de Vineni VR, Harvey J, et al. The risk of contralateral and lymphatic metastases for cancers of the larynx and pharynx. *Am J Otolaryngol* 1992; 13:134–39.
60. Levendag P, Sessions R, Vikram B, et al. The problem of neck relapse in early supraglottic larynx cancer. *Cancer* 1989; 63:345–348.
61. Myers EN, Alvi A. Management of carcinoma of the supraglottic larynx: Evolution, current concepts, and future trends. *Laryngoscope* 1996; 106:559–567.
62. Chiu RJ, Myers EN, Johnson JT. Efficacy of routine bilateral neck dissection in the management of supraglottic carcinoma. *Otolaryngol Head Neck Surg* 2004; 131:485–488.
63. Zeitels SM, Davis R Kim. Endoscopic laser management of supraglottic carcinoma. *Am J Otolaryngol* 1995; 16:2–11.
64. Department of Veterans Affairs Laryngeal Cancer Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991; 324:1685–1690.
65. Sessions DG, Lenox J, Spector GJ. Supraglottic laryngeal cancer: Analysis of treatment results. *Laryngoscope* 2005; 115:1402–1410.
66. Probert JC, Thompson RW, Bagshaw MA. Patterns of spread of distant metastases in head and neck cancer. *Cancer* 1974; 33:127–133.
67. Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer* 1977; 40:145–151.
68. Nadol JB Jr. Treatment of carcinoma of the epiglottis. *Ann Otol Rhinol Laryngol* 1981; 90:442–448.
69. Prades J-M, Simon P-G, Timoshenko AP, et al. Extended and standard supraglottic laryngectomies: a review of 110 patients. *Eur Arch Otorhinolaryngol* 2005; 262:947–952.
70. Taskinen PJ. The early case of supraglottic carcinoma. *Laryngoscope* 1975; 85:1643–1649.
71. Cachin Y. Supraglottic carcinomas: the early cases. *Laryngoscope* 1975; 85:1617–1623.
72. Laccourreye H, Brasnu DF, Beutter P. Carcinoma of the laryngeal margin. *Head Neck Surg* 1983; 5:500–507.
73. Staff PM, Gregory I, Watt J. Morphometry of the epithelial lining of the human larynx. *Clin Otolaryngol* 1978; 3:13–20.
74. van Nostrand AWP. Classification, anatomy, growth, and spread of laryngeal cancer. In: Alberti PW, Bryce DP, eds. *Centennial Conference on Laryngeal Cancer*. New York: Appleton-Century-Crofts, 1976:2–4.
75. Daly CJ, Strong EW. Carcinoma of the glottic larynx. *Am J Surg* 1975; 130:489–492.
76. Sessions DG, Ogura JH, Fried MP. The anterior commissure in glottic carcinoma. *Laryngoscope* 1975; 85:1624–1632.
77. Olofsson J. Specific features of laryngeal carcinoma involving the anterior commissure and the subglottic region. *Can J Otolaryngol* 1975; 4:618–632.
78. Rothfield RE, Johnson JT, Myers EN, et al. The role of hemilaryngectomy in management of T1 vocal cord cancer. *Arch Otolaryngol Head Neck Surg* 1989; 115:677–680.
79. Werner JA, Schunke MN, Rudert H, et al. Description and clinical importance of the lymphatics of the vocal fold. *Otolaryngol Head Neck Surg* 1990; 102:13–19.
80. Nassar VH, Bridger GP. Topography of the laryngeal mucous glands. *Arch Otolaryngol* 1971; 94:490–498.
81. Kirchner JA, Som JL. Clinical significance of fixed vocal cord. *Laryngoscope* 1971; 81:1029–1044.
82. Mendonca DR, Bryce DP. Transglottic cancer of the larynx—a case presentation. *Can J Otolaryngol* 1973; 2:271–276.
83. Kirchner JA. Two-hundred laryngeal cancers: patterns of growth and spread as seen in serial section. *Laryngoscope* 1977; 87:474–482.
84. Foote RL, Buskirk SJ, Stanley RJ, et al. Patterns of failure after total laryngectomy for glottic carcinoma. *Cancer* 1989; 64:143–149.
85. Johnson JT, Myers EN, Hao S-P, et al. Outcome of open surgical therapy for glottic carcinoma. *Ann Otol Rhinol Laryngol* 1993; 102:752–755.
86. Thomas JV, Olsen KD, Neel HB III, et al. Early glottic carcinoma treated with open procedures. *Arch Otolaryngol Head Neck Surg* 1994; 120:264–269.
87. Yuen A, Medina JE, Goepfert H, et al. Management of stage T3 and T4 glottic carcinomas. *Am J Surg* 1984; 148:467–472.
88. Lundgren JAV, Gilbert RW, van Nostrand AWP, et al. T₁N₀M₀ glottic carcinoma—a failure analysis. *Clin Otolaryngol* 1988; 13:455–465.
89. Stell PM, Tobin KE. The behavior of cancer affecting the subglottic space. *Can J Otolaryngol* 1975; 4:612–617.
90. Vermund H. Role of radiotherapy in cancer of the larynx as related to the TNM system of staging. A review. *Cancer* 1970; 25:485–504.
91. Harrison DFN. The pathology and management of subglottic cancer. *Ann Otol Rhinol Laryngol* 1971; 80:6–12.
92. Bryce DP. The laryngeal subglottis. *J Laryngol Otol* 1975; 89:667–685.
93. Sessions DG, Ogura JH, Fried MP. Carcinoma of the subglottic area. *Laryngoscope* 1975; 85:1417–1423.
94. Shaha AR, Shah JP. Carcinoma of the subglottic larynx. *Am J Surg* 1982; 144:456–458.
95. Warde P, Harwood A, Keane T. Carcinoma of the subglottis. Results of initial radical treatment. *Arch Otolaryngol Head Neck Surg* 1987; 113:1228–1229.
96. Weber RS, Marvel J, Smith P, et al. Paratracheal lymph node dissection for carcinoma of the larynx, hypopharynx, and cervical esophagus. *Otolaryngol Head Neck Surg* 1992; 108:11–17.
97. Freeland AP, van Nostrand AWP. The applied anatomy of the anterior commissure and subglottis. *Can J Otolaryngol* 1975; 4:644–658.
98. Dahm JD, Sessions DG, Paniello RC, et al. Primary subglottic cancer. *Laryngoscope* 1998; 108:741–746.
99. Garas J, McGuirt WF Sr. Squamous cell carcinoma of the subglottis. *Am J Otolaryngol* 2006; 27:1–4.
100. Mittal B, Marks JE, Ogura JH. Transglottic carcinoma. *Cancer* 1984; 53:151–161.
101. Kirchner JA, Cornog JL Jr., Holmes RE. Transglottic cancer. Its growth and spread within the larynx. *Arch Otolaryngol* 1974; 99:247–251.
102. Pittam MR, Carter RL. Framework invasion by laryngeal carcinomas. *Head Neck Surg* 1982; 4:200–208.
103. Jones DG, Gabriel CE. The incidence of carcinoma of the larynx in persons under twenty years of age. *Laryngoscope* 1969; 77:251–255.
104. Ossoff RH, Tucker GF, Norris CM. Carcinoma of the larynx in an 11-year-old boy with late cervical metastases: report of a case with a ten-year follow-up. *Otolaryngol Head Neck Surg* 1980; 88:142–145.
105. Gindhart TD, Johnston WH, Chism SE, et al. Carcinoma of the larynx in childhood. *Cancer* 1980; 46:1683–1687.

106. Hordijk GJ, de Jong JMA. Squamous carcinoma of the adolescent larynx. *Ear Nose Throat J* 1981; 60:25-28.
107. Laurian N, Sador R, Strauss M, et al. Laryngeal carcinoma in childhood. Report of a case and review of the literature. *Laryngoscope* 1984; 94:684-687.
108. Singh W, Kauer A. Laryngeal carcinoma in a six year old with a review of the literature. *J Laryngol Otol* 1987; 101:957-958.
109. Zalzal GH, Cotton RT, Bore K. Carcinoma of the larynx in a child. *Int J Pediatr Otorhinolaryngol* 1987; 13:219-225.
110. Chaput M, Ninane J, Gosseye S, et al. Juvenile laryngeal papillomatosis and epidermoid carcinoma. *J Pediatr* 1989; 114:269-272.
111. Amirghassem B, Wenig BM, Heffner DK, et al. Pediatric laryngeal squamous carcinomas (PLSQ). *Mod Pathol* 1993; 6:79A (abstr).
112. Simon M, Kahn T, Schneider A, et al. Laryngeal carcinoma in a 12-year-old child. Association with human papillomavirus 18 and 33. *Arch Otolaryngol Head Neck Surg* 1994; 120:277-282.
113. Futrell JW, Bennett SH, Hoyer RC, et al. Predicting survival in cancer of the larynx or hypopharynx. *Am J Surg* 1971; 122:451-457.
114. Bauer WC, Lesinski SG, Ogura JH. The significance of positive margins in hemilaryngectomy specimens. *Laryngoscope* 1975; 85:1-13.
115. Johnson JT, Myers EN, Bedetti CD, et al. Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. *Arch Otolaryngol* 1985; 111:534-537.
116. Synderman NL, Johnson JT, Schramm VL, et al. Extracapsular spread of carcinoma in cervical lymph nodes. Impact upon survival in patients with carcinoma of the supraglottic larynx. *Cancer* 1985; 56:1597-1599.
117. Johnson JT. A surgeon looks at cervical lymph nodes. *Radiology* 1990; 175:607-610.
118. Hirabayashi H, Koshii K, Uno K, et al. Extracapsular spread of squamous cell carcinoma in neck lymph nodes: prognostic factor of laryngeal cancer. *Laryngoscope* 1991; 101:502-506.
119. Dyess CL, Carter D, Kirchner JA. Morphometric comparison of the changes in the laryngeal skeleton associated with invasion by tumor and by external-beam radiation. *Cancer* 1987; 59:117-1122.
120. Kirchner JA. Invasion of the framework by laryngeal cancer. Surgical and radiological implications. *Acta Otolaryngol (Stockh)* 1984; 97:392-397.
121. Rubin J, Johnson JT, Myers EN. Stomal recurrence after laryngectomy: interrelated risk factor study. *Otolaryngol Head Neck Surg* 1990; 103:805-812.
122. Rockley TJ, Powell J, Robin PE, et al. Post-laryngectomy stomal recurrence: tumour implantation or paratracheal lymphatic metastases? *Clin Otolaryngol* 1991; 16:43-47.
123. Esteban F, Moreno JA, Delgado-Rodriguez M, et al. Risk factors involved in stomal recurrence following laryngectomy. *J Laryngol Otol* 1993; 107:527-531.
124. Gilbert RW, Cullen RJ, van Nostrand AWP, et al. Prognostic significance of thyroid gland involvement in laryngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 1986; 112:856-859.
125. Ogura JH. Surgical pathology of cancer of the larynx. *Laryngoscope* 1955; 65:867-926.
126. de Vries N, Snow GB. Multiple primary tumours in laryngeal cancer. *J Laryngol Otol* 1986; 100:915-918.
127. Silvestri F, Bussani R, Cosatti C, et al. High relative risk of a second pulmonary cancer in patients affected by laryngeal cancer: differences by specific site of occurrence and lung cancer histotype. *Laryngoscope* 1994; 104:222-225.
128. Haughey BH, Gates GA, Arfken CL, et al. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. *Ann Otol Rhinol Laryngol* 1992; 101:105-112.
129. Wagenfield DJH, Harwood AR, Bryce DP, et al. Second primary respiratory tract malignancies in glottic carcinoma. *Cancer* 1980; 46:1883-1886.
130. Wagenfield DJH, Harwood AR, Bryce DP, et al. Second primary respiratory tract malignant neoplasms in supraglottic carcinoma. *Arch Otolaryngol* 1981; 107:135-137.
131. Christensen P-H, Joergensen K, Munk J, et al. Hyperfrequency of pulmonary cancer in population of 415 patients treated for laryngeal cancer. *Laryngoscope* 1987; 97:612-614.
132. McGarry GW, Mackenzie EK. Second primary tumours of the larynx following bronchial carcinoma. *J Laryngol Otol* 1990; 104:629-630.
133. Goldsmith MM, Cresson DS, Postma DS, et al. Significance of ploidy in laryngeal cancer. *Am J Surg* 1986; 152:396-402.
134. Feinmesser R, Freeman JL, Noyek A. Flow cytometric analysis of DNA content in laryngeal cancer. *J Laryngol Otol* 1990; 104:485-487.
135. Stell PM. Ploidy in head and neck cancer: a review and meta-analysis. *Clin Otolaryngol* 1991; 16:510-516.
136. Rua S, Comino A, Fruttero A, et al. Relationship between histologic features, DNA flow cytometry, and clinical behavior of squamous cell carcinomas of the larynx. *Cancer* 1991; 67:141-149.
137. Walter MA, Peters GE, Peiper SC. Predicting radioresistance in early glottic squamous cell carcinoma by DNA content. *Ann Otol Rhinol Laryngol* 1991; 100:523-526.
138. El-Naggar AK, Lopez-Varela V, Luna MA, et al. Intratumoral DNA content heterogeneity in laryngeal squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* 1992; 118:169-173.
139. Guo Y-C, DeSanto L, Osetinsky GV. Prognostic implication of nuclear DNA content in head and neck cancer. *Otolaryngol Head Neck Surg* 1989; 100:95-98.
140. Sakr W, Hussan M, Zarbo RJ, et al. DNA quantitation and histologic characteristics of squamous cell carcinoma of the upper aerodigestive tract. *Arch Pathol Lab Med* 1989; 113:1009-1014.
141. Campbell BH, Schemmel JC, Hopwood LE, et al. Flow cytometric evaluation of chemosensitive and chemoresistant head and neck tumors. *Am J Surg* 1990; 160:424-426.
142. Tennvall J, Wennerberg J, Anderson H, et al. DNA analysis as a predictor of the outcome of induction chemotherapy in advanced head and neck carcinomas. *Arch Otolaryngol Head Neck Surg* 1993; 119:867-870.
143. Kropveld A, Slootweg PJ, van Mansfield A DM, et al. Radioresistance and p53 status of T2 laryngeal carcinoma. Analysis by immunohistochemistry and denaturing gradient gel electrophoresis. *Cancer* 1996; 78:991-997.
144. Lera J, Lara PC, Perez S, et al. Tumor proliferation, p53 expression, and apoptosis in laryngeal carcinoma. Relation to the results of radiotherapy. *Cancer* 1998; 83:2493-2501.
145. Sittel C, Eckel HE, Damm M, et al. Ki-67 (MIB1), p53, and Lewis-X (LeuM1) as prognostic factors of recurrence in T1 and T2 laryngeal carcinoma. *Laryngoscope* 2000; 110:1012-1017.
146. Eriksen JG, Buffa FM, Alsner J, et al. Molecular profiles as predictive marker for the effect of overall treatment time of radiotherapy in supraglottic larynx squamous cell carcinoma. *Radiother Oncol* 2004; 72:275-282.
147. Valente G, Orecchia R, Gandolfo S, et al. Can Ki-67 immunostaining predict response to radiotherapy in oral squamous cell carcinoma? *J Clin Pathol* 1994; 47:109-112.
148. Raybaud-Diogene H, Fortin A, Morency R, et al. Markers of radioresistance in squamous cell carcinoma of the head

and neck: a clinicopathologic and immunohistochemical study. *J Clin Oncol* 1997; 15:1030-1038.

149. Roland NJ, Caslin AW, Bowie GL, et al. Has the cellular proliferation marker Ki-67 any clinical relevance in squamous cell carcinoma of the head and neck? *Clin Otolaryngol* 1994; 19:13-18.
- XV. SPINDLE CELL CARCINOMA, SARCOMATOID CARCINOMA, CARCINOSARCOMA**
1. Lane N. Pseudosarcoma (polypoid sarcoma-like masses) associated with squamous-cell carcinoma of the mouth, fauces, and larynx. Report of ten cases. *Cancer* 1957; 10:19-41.
 2. Battifora H. Spindle cell carcinoma. Ultrastructural evidence of squamous origin and collagen production by the tumor cells. *Cancer* 1976; 37:2275-2282.
 3. Brodsky G. Carcino(pseudo)sarcoma of the larynx: the controversy continues. *Otolaryngol Clin North Am* 1984; 17:185-197.
 4. Klijanienko J, Viel P, Duvillard P, et al. True carcinosarcoma of the larynx. *J Laryngol Otol* 1992; 106:58-60.
 5. Leifer C, Miller AS, Putong PB, et al. Spindle cell carcinoma of the oral mucosa: a light and electron microscopic study of apparent sarcomatous metastasis to cervical lymph nodes. *Cancer* 1976; 34:597-605.
 6. Martin MR, Kahn LB. So-called pseudosarcoma of the esophagus: nodal metastases of the spindle cell element. *Arch Pathol Lab Med* 1977; 101:604-609.
 7. Staley CJ, Ujiki GT, Yokoo H. "Pseudosarcoma" of the larynx: independent metastasis of carcinomatous and sarcomatous elements. *Arch Otolaryngol* 1971; 94:458-465.
 8. Sherwin RP, Strong MS, Vaugh CW Jr. Polypoid and junctional squamous cell carcinoma of the tongue and larynx with spindle cell carcinoma ("pseudosarcoma"). *Cancer* 1963; 16:51-60.
 9. Goellner JR, Devine KD, Weiland LH. Pseudosarcoma of the larynx. *Am J Clin Pathol* 1973; 59:312-326.
 10. Ellis GL, Langloss JM, Enzinger FM. Coexpression of keratin and desmin in a carcinosarcoma involving the maxillary alveolar ridge. *Oral Surg Oral Med Oral Pathol* 1985; 60:410-416.
 11. Humphrey PA, Scroggs MW, Roggli VL, et al. Pulmonary carcinomas with a sarcomatoid element: an immunocytochemical and ultrastructural analysis. *Hum Pathol* 1988; 19:155-165.
 12. Zarbo RJ, Crissman JD, Venkat H, et al. Spindle-cell carcinoma of the upper aerodigestive tract mucosa: an immunohistologic and ultrastructural study of 18 biphasic tumors and comparison with seven monophasic spindle-cell tumors. *Am J Surg* 1986; 10:741-753.
 13. Ellis GL, Langloss JM, Heffner DK, et al. Spindle-cell carcinoma of the aerodigestive tract. An immunohistochemical study of 21 cases. *Am J Surg Pathol* 1987; 11:335-342.
 14. Ro JY, Chen JL, Lee JS, et al. Sarcomatoid carcinoma of the lung. Immunohistochemical and ultrastructural studies of 14 cases. *Cancer* 1992; 69:376-386.
 15. Nakhleh RE, Zarbo RJ, Ewing S, et al. Myogenic differentiation in spindle cell (sarcomatoid) carcinomas of the upper aerodigestive tract. *Appl Immunohistochem* 1993; 1:58-68.
 16. Nappi O, Glasner SD, Swanson PE, et al. Biphasic and monophasic sarcomatoid carcinomas of the lung. A reappraisal of "carcinosarcomas" and "spindle-cell carcinomas." *Am J Clin Pathol* 1994; 102:331-340.
 17. Roncaroli F, Montironi R, Feliciotti F, et al. Sarcomatoid carcinoma of the anorectal junction with neuroendocrine and rhabdomyoblastic features. *Am J Surg Pathol* 1995; 19:217-223.
 18. Lewis JE, Olsen KD, Sebo TJ. Spindle cell carcinoma of the larynx: a pathologic analysis of 26 cases including DNA content and immunohistochemistry. *Lab Invest* 1995; 72:103A (abstr).
 19. Pearl GS, Mirra SS, Miles ML. Pseudosarcoma of the tongue: light and electron microscopic observations. *South Med J* 1980; 73:504-507.
 20. Lichtiger B, Mackey B, Tessmer CF. Spindle cell variant of squamous carcinoma: a light and electron microscopic study of 13 cases. *Cancer* 1970; 26:1311-1320.
 21. Rainosch DE, Ro JY, Ordonez NG, et al. Sarcomatoid carcinoma of the lung. A case with atypical carcinoid and rhabdomyosarcomatous components. *Am J Clin Pathol* 1994; 102:360-364.
 22. Leibl S, Gogg-Kammerer M, Andrea MT, et al. Metaplastic breast carcinomas: Are they of myoepithelial differentiation? Immunohistochemical profile of the sarcomatoid subtype using novel myoepithelial markers. *Am J Surg Pathol* 2005; 29:347-353.
 23. Thompson L, Chang B, Barsky SH. Monoclonal origins of malignant mixed tumors (carcinosarcomas). Evidence for a divergent histogenesis. *Am J Surg Pathol* 1996; 20:277-285.
 24. Wada H, Enomoto T, Tsujimoto M, et al. Carcinosarcoma of the breast: molecular- biological study for analysis of histogenesis. *Hum Pathol* 1998; 29:1324-1328.
 25. Ota S, Kato A, Kobayashi H, et al. Monoclonal origin of an esophageal carcinosarcoma producing granulocyte-colony stimulating factor. A case report. *Cancer* 1998; 82:2102-2111.
 26. Dacic S, Finklestein SD, Sasatomi E, et al. Molecular pathogenesis of pulmonary carcinosarcoma as determined by microdissection-based allelotyping. *Am J Surg Pathol* 2002; 26:510-516.
 27. Choi H-R, Sturgis EM, Rosenthal DI, et al. Sarcomatoid carcinoma of the head and neck. Molecular evidence for evolution and progression from conventional squamous cell carcinomas. *Am J Surg Pathol* 2003; 27:1216-1220.
 28. Arakawa A, Fujii H, Matsumoto T, et al. Loss of heterozygosity in clonal evolution with genetic progression and divergence in spindle cell carcinoma of the gallbladder. *Hum Pathol* 2004; 35:418-423.
 29. Pelosi G, Scarpa A, Manzotti M, et al. K-ras gene mutational analysis supports a monoclonal origin of biphasic pleomorphic carcinoma of the larynx. *Mod Pathol* 2004; 17:538-546.
 30. Miettinen M. Immunoreactivity for cytokeratin and epithelial membrane antigen in leiomyosarcomas. *Arch Pathol Lab Invest* 1988; 112:637-640.
 31. Gould VE. Histogenesis and differentiation: a reevaluation of these concepts as criteria for the classification of tumors. *Hum Pathol* 1986; 17:212-215.
 32. Mills SE. Editorial. Sometimes we don't look like our parents. *Mod Pathol* 1995; 8:347.
 33. Wick MR, Swanson PE. Carcinosarcomas: current perspectives and a historical review of nosological concepts. *Semin Diagn Pathol* 1993; 10:118-127.
 34. Nappi O, Wick MR. Sarcomatoid neoplasms of the respiratory tract. *Semin Diagn Pathol* 1993; 10:137-147.
 35. Lambert PR, Ward PH, Berei G. Pseudosarcoma of the larynx. A comprehensive analysis. *Arch Otolaryngol* 1980; 106:700-708.
 36. Leventon GS, Evans HL. Sarcomatoid squamous cell carcinoma of the mucous membranes of the head and

- neck. A clinicopathologic study of 20 cases. *Cancer* 1981; 48:994-1003.
37. Goldman RL, Weidner N. Pure squamous cell carcinoma of the larynx with cervical nodal metastasis showing rhabdomyosarcomatous differentiation. Clinical, pathologic, and immunohistochemical study of a unique example of divergent differentiation. *Am J Surg Pathol* 1993; 17:415-421.
 38. Wharton JM, Boguniewicz AB, Jennings TA. Sarcomatoid tumors of the upper respiratory tract after irradiation: a comparative study. *Am J Clin Pathol* 1994; 102:525 (abstr).
 39. Larsen ET, Duggan MA, Inque M. Absence of human papilloma virus DNA in oropharyngeal spindle-cell squamous carcinomas. *Am J Clin Pathol* 1994; 101:514-518.
 40. Ellis GL, Corio RL. Spindle cell carcinoma of the oral cavity. A clinicopathologic assessment of fifty-nine cases. *Oral Surg Oral Med Oral Pathol* 1980; 50:522-534.
 41. Leventon GS, Evans HL. Sarcomatoid squamous cell carcinoma of the mucous membranes of the head and neck. A clinicopathologic study of 20 cases. *Cancer* 1981; 48:994-1003.
 42. Berthelet E, Shenouda G, Black MJ, et al. Sarcomatoid carcinoma of the head and neck. *Am J Surg* 1994; 168:455-458.
 43. Olsen KD, Lewis JE, Suman VJ. Spindle cell carcinoma of the larynx and hypopharynx. *Otolaryngol Head Neck Surg* 1997; 116:47-52.
 44. Lewis JE, Olsen KD, Sebo TJ. Spindle cell carcinoma of the larynx: Review of 26 cases including DNA content and immunohistochemistry. *Hum Pathol* 1997; 28:664-673.
 45. Thompson LD, Wieneke JA, Miettinen M, et al. Spindle cell (sarcomatoid) carcinomas of the larynx. A clinicopathologic study of 187 cases. *Am J Surg Pathol* 2002; 26:153-170.
 46. Kessler S, Bartley MH. Spindle cell squamous carcinoma of the tongue in the first decade of life. *Oral Surg Oral Med Oral Pathol* 1988; 66:470-474.
 47. Matsusaka T, Watanabe H, Enjoji M. Pseudosarcoma and carcinoma of the esophagus. *Cancer* 1976; 37:1546-1555.
 48. Lewis JS Jr., Ritter JH, El-Mofty S. Alternative epithelial markers in sarcomatoid carcinoma of the head and neck, lung, and bladder – p63, MOC-31 and TTF-1. *Mod Pathol* 2005; 18:1471-1481.
 49. Zellers RA, Bickett WJ, Parker MG. Posttraumatic spindle cell nodule of the buccal mucosa. Report of a case. *Oral Surg Oral Med Oral Pathol* 1992; 74:212-215.
 50. Wenig BM, Devaney K, Biceglia M. Inflammatory myofibroblastic tumor of the larynx. A clinicopathologic study of eight cases simulating a malignant spindle cell neoplasm. *Cancer* 1995; 76:2217-2229.
 51. Baker PM, Young RH. Radiation-induced pseudosarcomatous proliferation of the urinary bladder: A report of 4 cases. *Hum Pathol* 2000; 31:678-683.
 52. Meehan SA, LeBoit PE. An immunohistochemical analysis of radiation fibroblasts. *J Cutan Pathol* 1997; 24:309-313.
 53. Ansari-Lari MA, Hoque MO, Califano J, et al. Immunohistochemical p53 expression patterns in sarcomatoid carcinomas of the upper respiratory tract. *Am J Surg Pathol* 2002; 26:1024-1031.
 54. Davis WG, Hennessy B, Babiera G, et al. Metaplastic sarcomatoid carcinoma of the breast with absent or minimal overt invasive carcinomatous component. A misnomer. *Am J Surg Pathol* 2005; 29:1456-1463.
 5. Ferlito A, Rechner G. Ackerman's tumor (verrucous carcinoma) of the larynx. A clinicopathologic study of 77 cases. *Cancer* 1986; 46:1617-1630.
 4. Cardeza A, Zidar N. Verrucous carcinoma. In: Barnes L, Everson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours. Pathology and Genetics, Head and Neck Tumours*. Lyon, France: IARC Press, 2005:122-123.
 5. Kraus FT, Perez-Mesa C. Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx, and genitalia. *Cancer* 1966; 19:26-38.
 6. Ferlito A. Diagnosis and treatment of verrucous squamous cell carcinoma of the larynx: a critical review. *Ann Otol Rhinol Laryngol* 1985; 94:575-579.
 7. Maw AR, Cullen RJ, Bradfield JWB. Verrucous carcinoma of the larynx. *Clin Otolaryngol* 1982; 7:305-311.
 8. Lundgren JAV, van Nostrand AWP, Harwood AR, et al. Verrucous carcinoma (Ackerman's tumor) of the larynx: diagnostic and therapeutic considerations. *Head Neck Surg* 1986; 9:19-26.
 9. Edstrom S, Johansson SL, Lindstrom J, et al. Verrucous squamous cell carcinoma of the larynx: evidence for increased metastatic potential after irradiation. *Otolaryngol Head Neck Surg* 1987; 97:381-384.
 10. Milford CA, O'Flynn PE. Management of verrucous carcinoma of the larynx. *Clin Otolaryngol* 1991; 16:160-160.
 11. Silamniko B, Bauer W, Painter C, et al. Clinical and histopathological considerations for the diagnosis and treatment of verrucous carcinoma of the larynx. *Arch Otorhinolaryngol* 1989; 246:126-132.
 12. Orvidas LJ, Olsen KD, Lewis JE, et al. Verrucous carcinoma of the larynx: a review of 53 patients. *Head Neck* 1998; 20:197-203.
 13. Koch BB, Trask DK, Hoffman HT, et al. National survey of head and neck verrucous carcinoma. Patterns of presentation, care and outcome. *Cancer* 2001; 92:110-120.
 14. McCaffrey TV, Witte M, Ferguson MT. Verrucous carcinoma of the larynx. *Ann Otol Rhinol Laryngol* 1998; 107:391-395.
 15. Brandsma JL, Steinberg BM, Abramson AL, et al. Presence of human papillomavirus type 16 related sequences in verrucous carcinoma of the larynx. *Cancer Res* 1986; 46:2185-2188.
 16. Bryan RL, Bevan IS, Crocker J, et al. Detection of HPV 6 and 11 in tumors of the upper respiratory tract using the polymerase chain reaction. *Clin Otolaryngol* 1990; 15:177-180.
 17. Johnson TL, Plieth DA, Crissman JD, et al. HPV detection by polymerase chain reaction (PCR) in verrucous lesions of the upper aerodigestive tract. *Mod Pathol* 1991; 4:461-465.
 18. Kasperbauer JL, O'Halloran GL, Espy MJ, et al. Polymerase chain reaction (PCR) identification of human papillomavirus (HPV) DNA in verrucous carcinoma of the larynx. *Laryngoscope* 1993; 103:416-420.
 19. Fliss DM, Noble-Topham SE, McLachlin CM, et al. Laryngeal verrucous carcinoma: a clinicopathologic study and detection of human papillomavirus using polymerase chain reaction. *Laryngoscope* 1994; 104:146-152.
 20. Medina JE, Dichtel W, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathologic study of 104 cases. *Arch Otolaryngol* 1984; 110:437-440.
 21. Lopez-Amado M, Garcia-Caballero T, Lozano-Ramirez A, et al. Human papillomavirus and p53 oncoprotein in verrucous carcinoma of the larynx. *J Laryngol Otol* 1996; 110:742-747.
 22. Sakurai K, Urade M, Takahashi Y, et al. Increased expression of C-erbB-3 protein and proliferating nuclear antigen during development of verrucous carcinoma of the oral mucosa. *Cancer* 2000; 89:2597-2605.

XVI. VERRUCOUS CARCINOMA

23. Choi HR, Roberts DB, Johnigan RH, et al. Molecular and clinicopathologic comparisons of head and neck squamous carcinoma variants. Common and distinctive features of biological significance. *Am J Surg Pathol* 2004; 28:1299–1310.
24. Poh CF, Zhang L, Lam WL, et al. A high frequency of allelic loss in oral verrucous lesions may explain malignant risk. *Lab Invest* 2001; 81:629–634.
25. Maurizi M, Cadoni G, Ottaviani F, et al. Verrucous squamous cell carcinoma of the larynx: diagnostic and therapeutic considerations. *Eur Arch Otorhinolaryngol* 1996; 253:130–135.
26. Ferlito A, Rinaldo A, Mannara GM. Is primary radiotherapy an appropriate option for the treatment of verrucous carcinoma of the head and neck? *J Laryngol Otol* 1998; 112:132–139.
27. McClure DL, Gullane PJ, Slinger RP, et al. Verrucous carcinoma—changing concepts in management. *J Otolaryngol* 1984; 13:7–12.
28. Hagen P, Lyons GD, Haindel C. Verrucous carcinoma of the larynx: role of human papillomavirus, radiation, and surgery. *Laryngoscope* 1993; 103:253–257.
29. Batsakis JG, Hybels R, Crissman JD, et al. The pathology of head and neck tumors: verrucous carcinoma, part 15. *Head Neck Surg* 1982; 5:29–38.
30. Glanz H, Kleinsasser O. Verrucous carcinoma of the larynx—a misnomer? *Arch Otorhinolaryngol* 1987; 244:108–111.
3. Wan SK, Chan JKC, Tse KC. Basaloid-squamous carcinoma of the nasal cavity. *J Laryngol Otol* 1992; 106:370–371.
4. Lovejoy HM, Matthews BL. Basaloid-squamous carcinoma of the palate. *Otolaryngol Head Neck Surg* 1992; 106:159–162.
5. Cadier MA, Kelly SA, Parkhouse N, et al. Basaloid squamous carcinoma of the buccal cavity. *Head Neck* 1992; 14:387–391.
6. Banks ER, Frierson HF Jr., Mills SE, et al. Basaloid squamous cell carcinoma of the head and neck. A clinicopathologic and immunohistochemical study of 40 cases. *Am J Surg Pathol* 1992; 16:939–946.
7. Coppola D, Catalano E, Tang C-K, et al. Basaloid squamous cell carcinoma of the floor of mouth. *Cancer* 1993; 72:2299–2305.
8. Luna MA, El-Naggar A, Parichatikanond P, et al. Basaloid squamous carcinoma of the upper aerodigestive tract. Clinicopathologic and DNA flow cytometric analysis. *Cancer* 1990; 66:537–542.
9. Ereno C, Lopez JI, Sanchez JM, et al. Basaloid-squamous cell carcinoma of the larynx and hypopharynx. A clinicopathologic study of 7 cases. *Path Res Pract* 1994; 190:186–193.
10. Wieneke JA, Thompson LDR, Wenig BM. Basaloid squamous cell carcinoma of the sinonasal tract. *Cancer* 1999; 85:841–854.
11. Ide F, Shimoyama T, Horie N, et al. Basaloid squamous cell carcinoma of the oral mucosa: a new case and review of 45 cases in the literature. *Oral Oncol* 2002; 38:120–124.
12. Bahar G, Feinmesser R, Popovtzer A, et al. Basaloid squamous carcinoma of the larynx. *Am J Otolaryngol* 2003; 24:204–208.
13. Grizzo de Sampaio Goes FC, Oliveira DT, Dorta RG, et al. Prognoses of oral basaloid squamous cell carcinoma and squamous cell carcinoma. A comparison. *Arch Otolaryngol Head Neck Surg* 2004; 130:83–86.
14. Dougherty BG, Evans HL. Carcinoma of the anal canal: a study of 79 cases. *Am J Clin Pathol* 1985; 83:159–164.
15. Tsang WYW, Chan JKC, Lee KC, et al. Basaloid-squamous carcinoma of the upper aerodigestive tract and so-called adenoid cystic carcinoma of the esophagus: the same tumour type? *Histopathology* 1991; 19:35–46.
16. Ferry JA, Scully RE. “Adenoid cystic” carcinoma and adenoid basal cell carcinoma of the uterine cervix: a study of 28 cases. *Am J Surg Pathol* 1988; 12:134–144.
17. Moro D, Brichon P-Y, Brambilla E, et al. Basaloid bronchial carcinoma. A histologic group with a poor prognosis. *Cancer* 1994; 73:2734–2739.
18. Sturm N, Lantuejoul S, Laverriere M-H, et al. Thyroid transcription factor 1 and cytokeratins 1, 5, 10, 14 (34BE12) expressions in basaloid and large-cell neuroendocrine carcinomas of the lung. *Hum Pathol* 2001; 32:918–925.
19. Abe K, Sasano H, Itakura Y, et al. Basaloid-squamous carcinoma of the esophagus. A clinicopathologic, DNA ploidy, and immunohistochemical study of seven cases. *Am J Surg Pathol* 1996; 20:453–461.
20. Cubilla AL, Reuter VE, Gregoire L, et al. Basaloid squamous cell carcinoma: A distinctive human papilloma virus-related penile neoplasm. A report of 20 cases. *Am J Surg Pathol* 1998; 22:755–761.
21. Chetty R, Serra S, Hsieh E. Basaloid squamous carcinoma of the anal canal with an adenoid cystic pattern. Histologic and immunohistochemical reappraisal of an unusual variant. *Am J Surg Pathol* 2005; 29:1668–1672.
22. Wak S-K, Chan JKC, Lau W-H, et al. Basaloid squamous carcinoma of the nasopharynx: An Epstein-Barr virus associated neoplasm compared with morphologically identical tumors occurring in other sites. *Cancer* 1995; 76:1689–1693.

XVII. PAPILLARY SQUAMOUS CELL CARCINOMA

1. Ishiyama A, Eversole LR, Ross DA, et al. Papillary squamous neoplasms of the head and neck. *Laryngoscope* 1994; 104:1446–1452.
2. Thompson LDR, Wenig BM, Heffner DK, et al. Exophytic and papillary squamous cell carcinoma of the larynx: A clinicopathologic series of 104 cases. *Otolaryngol Head Neck Surg* 1999; 120:718–724.
3. Suarez PA, Adler-Storthz K, Luna MA, et al. Papillary squamous cell carcinomas of the upper aerodigestive tract: A clinicopathologic and molecular study. *Head Neck* 2000; 22:360–368.
4. Ereno C, Lopez JI, Sanchez JM, et al. Papillary squamous cell carcinoma of the larynx. *J Laryngol Otol* 2001; 115:164–166.
5. Crissman JD, Kessis T, Shah KV, et al. Squamous papillary neoplasia of the upper aerodigestive tract. *Hum Pathol* 1988; 19:1387–1396.
6. Judd R, Zaki SR, Coffield LM, et al. Human Papillomavirus type 6 detected by the polymerase chain reaction in invasive sinonasal papillary squamous cell carcinoma. *Arch Pathol Lab Med* 1991; 115:1150–1153.
7. Quick CA, Foucer E, Dehner CP. Frequency and significance of epithelial dysplasia in laryngeal papillomatosis. *Laryngoscope* 1979; 89:550–560.

XVIII. BASALOID SQUAMOUS CELL CARCINOMA

1. Wain SL, Kier R, Vollmer RT, et al. Basaloid squamous carcinoma of the tongue, hypopharynx, and larynx: report of 10 cases. *Hum Pathol* 1986; 17:1158–1166.
2. Raslan WF, Barnes L, Krause JR, et al. Basaloid squamous cell carcinoma of the head and neck: a clinicopathologic and flow cytometric study of 10 new cases with review of the English literature. *Am J Otolaryngol* 1994; 15:204–211.

23. Vincent-Salomon A, de la Rochefordiere A, Salmon R, et al. Frequent association of human papillomavirus 16 and 18 DNA with anal squamous cell and basaloid carcinoma. *Mod Pathol* 1996; 9:614-620.
24. Gregoire L, Cubilla AL, Reuter VE, et al. Preferential association of human papillomavirus with high grade histologic variants of penile-invasive squamous cell carcinoma. *J Natl Cancer Inst* 1995; 87:1705-1709.
25. Sheikh H, Fishera M, Hunt JL. Basaloid squamous cell carcinoma of the head and neck: Analysis of p53 and HPV in 46 cases. *Mod Pathol* 2004; 17:233A (abstr).
26. Kleist B, Bankau A, Lorenz G, et al. Different risk factors in basaloid and common squamous head and neck cancer. *Laryngoscope* 2004; 114:1063-1068.
27. Muller S, Barnes L. Basaloid squamous cell carcinoma of the head and neck with a spindle cell component. An unusual histologic variant. *Arch Pathol Lab Med* 1995; 119:181-182.
28. Kimura T, Mukai M, Shiotani A, et al. Basaloid squamous carcinoma of the hypopharynx with extensive spindle cell component exhibiting a pedunculated polypoid mass. *Arch Pathol Lab Med* 2005; 129:e94-e96.
29. Amatya VJ, Takeshima Y, Kaneko M, et al. Esophageal carcinosarcoma with basaloid squamous carcinoma and rhabdomyosarcoma components with TP53 mutation. *Pathol Int* 2004; 54:803-809.
30. Klijanienko J, El-Naggar A, Ponzi-Prion A, et al. Basaloid squamous carcinoma of the head and neck. Immunohistochemical comparison with adenoid cystic carcinoma and squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* 1993; 119:887-896.
31. Morice WG, Ferreiro JA. Distinction of basaloid squamous cell carcinoma from adenoid cystic and small cell undifferentiated carcinoma by immunohistochemistry. *Hum Pathol* 1998; 29:609-612.
32. Mino M, Pilch BZ, Faquin WC. Expression of KIT (CD117) in neoplasms of the head and neck: An ancillary marker for adenoid cystic carcinoma. *Mod Pathol* 2003; 16:1224-1231.
33. Emmanuel P, Wang B, Wu M, et al. P63 immunohistochemistry in the distinction of adenoid cystic carcinoma from basaloid squamous cell carcinoma. *Mod Pathol* 2005; 18:645-650.
34. Lantuejoul S, Faure C, Righini C, et al. Basaloid squamous cell carcinoma of the head and neck: Histological and immunohistochemical analysis of 47 cases. *Mod Pathol* 2004; 17:227A (abstr).
35. Akyol MU, Dursun A, Akyol G, et al. Proliferating cell nuclear antigen immunoreactivity and the presence of p53 mutation in basaloid squamous cell carcinoma of the larynx. *Oncology* 1998; 55:382-383.
36. Rodriguez Tojo MJ, Garcia Cano FJ, Infante Sanchez JC, et al. Immunoreexpression of p53, Ki-67 and E-cadherin in basaloid squamous cell carcinoma of the larynx. *Clin Transl Oncol* 2005; 7:110-114.
37. Krassilnik N, Ghali V, Wenig BM. Myoepithelial expression in basaloid squamous cell carcinoma of the head and neck (BSCC): An immunohistochemical (IHC) analysis. *Mod Pathol* 2004; 17:226A (abstract).
38. Seidman JD, Berman JJ, Yost BA, et al. Basaloid squamous carcinoma of the hypopharynx and larynx associated with second primary tumors. *Cancer* 1991; 68:1545-1549.
39. McKay MJ, Bilous AM. Basaloid-squamous carcinoma of the hypopharynx. *Cancer* 1989; 63:2528-2531.
2. Evans HL. Mucoepidermoid carcinoma of salivary glands: A study of 69 cases with special attention to histologic grading. *Am J Clin Pathol* 1984; 81:696-701.
3. Martinez-Madrigel F, Baden E, Casiraghi O, et al. Oral and pharyngeal adenosquamous carcinoma. A report of four cases with immunohistochemical studies. *Eur Arch Otorhinolaryngol* 1991; 248:255-258.
4. Fujino K, Ito J, Kanaji M, et al. Adenosquamous carcinoma of the larynx. *Am J Otolaryngol* 1995; 16:115-118.
5. Abdelsayed RA, Sanguenza OP, Newhouse RF, et al. Adenosquamous carcinoma. A case report with immunohistochemical evaluation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85:173-177.
6. Keelawat S, Liu CZ, Roehm PC, et al. Adenosquamous carcinoma of the upper aerodigestive tract: A clinicopathologic study of 12 cases and review of the literature. *Am J Otolaryngol* 2002; 23:160-168.
7. Alos L, Castillo M, Nadal A, et al. Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases. *Histopathology* 2004; 44:570-579.
8. Siar CH, Ng NH. Adenosquamous carcinoma of the floor of the mouth and lower alveolus: A radiation-induced lesion? *Oral Surg Oral Med Oral Pathol* 1987; 63:216-220.
9. Spiro RH, Huvos AG, Berk R, et al. Mucoepidermoid carcinoma of salivary gland origin: A clinicopathologic study of 367 cases. *Am J Surg* 1978; 136:461-468.
10. Gaertner EM, Wieneke JA, Wenig BM. Adenosquamous carcinoma (ASC) of the head and neck: A clinicopathologic study of 32 cases. *Mod Pathol* 1994; 12:128A (abstract).

XX. ACANTHOLYTIC SQUAMOUS CELL CARCINOMA

1. Cardesa A, Zidar N, Alos L. Acantholytic squamous cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours. Pathology and Genetics, Head and Neck Tumours*. Lyon, France: IARC Press, 2005:129.
2. Johnson WC, Helwig EB. Adenoid squamous cell carcinoma (adenoacanthoma): A clinicopathologic study of 155 patients. *Cancer* 1966; 19:1639-1650.
3. Nappi O, Wick MR, Pettinato G, et al. Pseudovascular adenoid squamous cell carcinoma of the skin. A neoplasm that may be mistaken for angiosarcoma. *Am J Surg Pathol* 1992; 16:429-438.
4. Takagi M, Sakota Y, Takayama et al. Adenoid squamous cell carcinoma of the oral mucosa. Report of two autopsy cases. *Cancer* 1977; 40:2250-2255.
5. Zaatari GS, Santoianni RA. Adenoid squamous cell carcinoma of the nasopharynx and neck region. *Arch Pathol Lab Med* 1986; 110:542-546.
6. Hertenstein JC, Fechner RE. Acantholytic squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* 1986; 112:780-783.
7. Basatkis JG, Huser J. Squamous carcinoma with gland-like (adenoid) features. *Ann Otol Rhinol Laryngol* 1990; 99:87-88.
8. Jones AC, Freedman PD, Kerpel SM. Oral adenoid squamous cell carcinoma: A report of three cases and review of the literature. *J Oral Maxillofac Surg* 1993; 51:676-681.
9. Ferlito A, Devaney KO, Rinaldo A, et al. Mucosal adenoid squamous cell carcinoma of the head and neck. *Ann Otol Rhinol Laryngol* 1996; 105:409-413.
10. Wenig BM. Squamous cell carcinoma of the upper aerodigestive tract: Precursor and problematic variants. *Mod Pathol* 2002; 15:229-254.
11. Stelow EB, Mills SE. Squamous cell carcinoma variants of the upper aerodigestive tract. *Am J Clin Pathol* 2005 (suppl) S96-S109.

XIX. ADENOSQUAMOUS CARCINOMA

1. Gerughty RM, Hennigam GR, Brown FM. Adenosquamous carcinoma of the nasal, oral, and laryngeal cavities. A clinicopathologic study of 10 cases. *Cancer* 1968; 22:1140-1154.

12. Kusafuka K, Ebihara M, Ishiki H, et al. Primary adenoid squamous cell carcinoma of the oral cavity. *Pathol Int* 2006; 56:78–83.

XXI. LYMPHOEPITHELIAL CARCINOMA

1. Tsang WYW, Chan JKC. Lymphoepithelial carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours. Pathology and Genetics, Head and Neck Tumours*. Lyon: IARC Press, 2005:132.
2. Ferlito A. Primary lymphoepithelial carcinoma of the hypopharynx. *J Laryngol Otol* 1977; 91:361–367.
3. Micheau C, Luboinski B, Schwaab G, et al. Lymphoepitheliomas of the larynx (undifferentiated carcinomas of nasopharyngeal type). *Clin Otolaryngol* 1979; 4:43–48.
4. Marioni G, Mariuzzi L, Gaio E, et al. Lymphoepithelial carcinoma of the larynx. *Acta Otolaryngol* 2002; 122:429–434.
5. MacMillan C, Kapadia SB, Finklestein SD, et al. Lymphoepithelial carcinoma of larynx and hypopharynx: study of eight cases with relationship to Epstein-Barr virus and p53 gene alterations, and review of the literature. *Hum Pathol* 1996; 27:1172–1179.

XXII. GIANT CELL CARCINOMA

1. Shanmugaratnam K, Sobin, Barnes L, et al. *World Health Organization International Histological Classification of Tumours. Histological Typing of Tumours of the Upper Respiratory Tract and Ear*. 2nd ed. New York: Springer-Verlag, 1991.
2. Wang N-S, Seemayer TA, Ahmed MN, et al. Giant cell carcinoma of the lung. A light and electron microscopic study. *Hum Pathol* 1976; 7:3–16.
3. Ginsberg SS, Buzaid A, Stern H, et al. Giant cell carcinoma of the lung. *Cancer* 1992; 70:606–610.
4. Fishback NF, Travis WD, Moran CA, et al. Pleomorphic (spindle/giant cell) carcinoma of the lung. A clinicopathologic correlation of 78 cases. *Cancer* 1994; 73:2936–2945.
5. Hammar SP. Common neoplasms. In: Dail DH, Hammar SP, Colby TV, eds. *Pulmonary Pathology—Tumors*. New York: Springer-Verlag, 1995:1–156.
6. Ferlito A, Friedmann J, Recher G. Primary giant cell carcinoma of the larynx. A clinico- pathological study of four cases. *ORL* 1985; 47:105–112.
7. Mackay B, Lukeman J, Ordonez N. *Tumors of the Lung*. Philadelphia: WB Saunders, 1991:101–103.
8. Martin PC, Hoda SA, Pigman HT, et al. Giant cell tumor of the larynx. Case report and review of the literature. *Arch Pathol Lab Med* 1994; 118:834–837.

XXIII. NEUROENDOCRINE TUMORS

1. Travis WD. The concept of pulmonary neuroendocrine tumours. In: Travis WD, Brambilla E, Muller-Hermelink HK, et al., eds. *World Health Organization Classification of Tumours, Pathology and Genetics, Tumours of the Lung, Pleura, Thymus, and Heart*. Lyon: IARC Press, 2004:19–20.
2. Barnes L. Neuroendocrine tumours in *World Health Organization Classification of Tumours, Pathology and Genetics, Head and Neck Tumours*, IARC Press, 2005: 135–139.
3. Ferlito A, Barnes L, Rinaldo A, et al. A review of neuroendocrine neoplasms of the larynx: update on diagnosis and treatment. *J Laryngol Otol* 1998; 112:827–834.

4. El-Naggar AK, Batsakis JG. Carcinoid tumor of the larynx. A critical review of the literature. *ORL J Otolaryngol Relat Spec* 1991; 53:189–193.
5. Woodruff JM, Senie RT. Atypical carcinoid tumor of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec* 1991; 53:194–209.
6. Gnepp DR. Small cell neuroendocrine carcinoma of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec* 1991; 53:210–219.
7. Barnes L. Paraganglioma of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec* 1991; 53:220–234.
8. Pesce C, Tobia-Gallelli F, Toncini C. APUD cells of the larynx. *Acta Otolaryngol* 1984; 98:158–162.
9. Chung J-H, Lee S-S, Shim Y-S, et al. A study of moderately differentiated neuroendocrine carcinomas of the larynx and an examination of non-neoplastic larynx tissue for neuroendocrine cells. *Laryngoscope* 2004; 114:1264–1270.
10. Wenig BM, Gnepp DR. The spectrum of neuroendocrine carcinomas of the larynx. *Semin Diagn Pathol* 1989; 6: 329–350.
11. Soga J, Ferlito A, Rinaldo A. Endocrinocarcinomas (carcinoids and their variants) of the larynx: a comparative consideration with those of other sites. *Oral Oncol* 2004; 40:668–672.
12. Synderman C, Johnson JT, Barnes L. Carcinoid tumor of the larynx: case report and review of the world literature. *Otolaryngol Head Neck Surg* 1986; 95:158–164.
13. Stanley RJ, DeSanto LW, Weiland LH. Oncocytic and oncocytoid carcinoid tumors (well-differentiated neuroendocrine carcinoma) of the larynx. *Arch Otolaryngol Head Neck Surg* 1986; 112:529–535.
14. Schmidt U, Metz KA, Schrader M, et al. Well-differentiated (oncocytoid) neuroendocrine carcinoma of the larynx with multiple skin metastases: a brief report. *J Laryngol Otol* 1994; 108:272–274.
15. Ferlito A, Shaha AR, Rinaldo A. Neuroendocrine neoplasms of the larynx: Diagnosis, treatment and prognosis. *ORL J Otorhinolaryngol Relat Spec* 2002; 64:108–113.
16. Goldman NC, Hood CI, Singleton GT. Carcinoid of the larynx. *Arch Otolaryngol* 1969; 90:91–93.
17. Andrews TM, Myer CM III. Malignant (atypical) carcinoid of the larynx occurring in a patient with laryngotracheal papillomatosis. *Am J Otolaryngol* 1992; 13:238–242.
18. Ferlito A, Shaha AR, Rinaldo A. Paraneoplastic syndrome in neuroendocrine neoplasms of the head and neck: Have they an impact on prognosis? *Acta Otolaryngol* 2001; 121:756–758.
19. Sweeney EC, McDonnell L, O'Brien C. Medullary carcinoma of the thyroid presenting as tumors of the pharynx and larynx. *Histopathology* 1981; 5:263–271.
20. Smets G, Warson F, Dehou M-F, et al. Metastasizing neuroendocrine carcinoma of the larynx with calcitonin and somatostatin secretion and CEA production, resembling medullary thyroid carcinoma. *Virchows Arch Pathol Anat* 1990; 416:539–543.
21. Laccourreye O, Chabardes E, Weinstein G, et al. Synchronous arytenoid and pancreatic neuroendocrine carcinoma. *J Laryngol Otol* 1991; 105:373–375.
22. Wenig BM, Hyams VJ, Heffner DK. Moderately differentiated neuroendocrine carcinoma of the larynx. A clinicopathologic study of 54 cases. *Cancer* 1988; 62:2658–2676.
23. Woodruff JM, Shah JP, Huvos AG, et al. Neuroendocrine carcinomas of the larynx. A study of two types, one of which mimics thyroid medullary carcinoma. *Am J Surg Pathol* 1985; 11:771–790.
24. Googe PB, Ferry JA, Bhan AK, et al. A comparison of paraganglioma, carcinoid tumor, and small-cell carcinoma of the larynx. *Arch Pathol Lab Med* 1988; 112:809–815.

25. Gillenwater A, Lewin J, Roberts D, et al. Moderately differentiated neuroendocrine carcinoma (atypical carcinoid of the larynx: A clinically aggressive tumor. *Laryngoscope* 2005; 115:1191-1195.
26. El-Naggar AK, Batsakis JG, Vassilopoulou-Sellin R, et al. Medullary (thyroid) carcinoma-like carcinoids of the larynx. *J Laryngol Otol* 1991; 105:683-686.
27. Sturm N, Rossi G, Lantuejoul S, et al. Expression of thyroid transcription factor-1 in the spectrum of neuroendocrine cell lung proliferation with special interest in carcinoids. *Hum Pathol* 2002; 33:175-182.
28. Hirsch MS, Faquin WC, Krane JF. Thyroid transcription factor-1, but not p53, is helpful in distinguishing moderately differentiated neuroendocrine carcinoma of the larynx from medullary carcinoma of the thyroid. *Mod Pathol* 2004; 17: 631-636.
29. Milroy CM, Williams RA, Charlton IG, et al. Nuclear ploidy in neuroendocrine neoplasms of the larynx. *ORL J Otorhinolaryngol Relat Spec* 1991; 53:245-249.
30. Olofsson J, van Nostrand AWP. Anaplastic small cell carcinoma of the larynx. Case report. *Ann Otol Rhinol Laryngol* 1972; 81:284-287.
31. Eusebi V, Damiani S, Pasquinelle G, et al. Small cell neuroendocrine carcinoma with skeletal muscle differentiation. Report of three cases. *Am J Surg Pathol* 2000; 24: 223-230.
32. Gnepp DR, Ferlito A, Hyams V. Primary anaplastic small cell (oat cell) carcinoma of the larynx. Review of the literature and report of 18 cases. *Cancer* 1983; 51:1731-1745.
33. Baugh RF, Wolf GT, Beals TF, et al. Small cell carcinoma of the larynx: results of treatment. *Laryngoscope* 1986; 96:1283-1290.
34. Trotoux J, Glickmanas M, Sterkers O, et al. Syndrome de Schwartz-Bartter: Relevateur d'un cancer larynge' sous-glottique a petites cellules. *Ann Otolaryngol Chir Cervicofac* 1979; 96:1720-1726.
35. Takeuchi K, Nishii S, Shun J, et al. Anaplastic small cell carcinoma of the larynx. *Auris Nasus Larynx* 1989; 16: 127-132.
36. Medina JE, Moran M, Goepfert H. Oat cell carcinoma of the larynx and Eaton-Lambert syndrome. *Arch Otolaryngol* 1984; 10:123-126.
37. Bishop JW, Osamura Y, Tsutsumi Y. Multiple hormone production in an oat cell carcinoma of the larynx. *Acta Pathol Jpn* 1985; 35:915-923.
38. Travis WD, Tsokos MG, Cutler GB Jr., et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural immunohistochemical, and flow-cytometric study of 35 cases. *Am J Surg Pathol* 1991; 15:529-553.
39. Greene L, Brundage W, Cooper K. Large cell neuroendocrine carcinoma of the larynx: a case report and a review of the classification of this neoplasm. *J Clin Pathol* 2005; 58:658-661.
40. Milroy CM, Robinson PJ, Grant HR. Primary composite squamous cell carcinoma and large cell neuroendocrine carcinoma of the hypopharynx. *J Laryngol Otol* 1989; 103: 1093-1096.
41. Asamura H, Kameya T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: A prognostic spectrum. *J Clin Oncol* 2006; 24:70-76.
42. Zacharias J, Nicolson AG, Ladas GP, et al. Large cell neuroendocrine carcinoma and large cell carcinoma with neuroendocrine morphology of the lung: prognosis after complete resection and systematic nodal dissection. *Ann Thorac Surg* 2003; 75:348-352.
43. Jaiswal VR, Hoang MP. Primary combined squamous and small cell carcinoma of the larynx. A case report and review of the literature. *Arch Pathol Lab Med* 2004; 128:1279-1282.

XXIV. SALIVARY GLAND-TYPE NEOPLASMS OF THE LARYNX

1. Cady B, Rippey JH, Frazell EL. Non-epidermoid cancer of the larynx. *Ann Surg* 1968; 167:116-120.
2. Batsakis JG, Luna MA, El-Naggar AK. Nonsquamous carcinomas of the larynx. *Ann Otol Rhinol Laryngol* 1992; 101:1024-1026.
3. Cotelingam JD, Barnes L, Nixon VB. Pleomorphic adenoma of the epiglottis. Report of a case. *Arch Otolaryngol* 1977; 103:245-247.
4. Dubey SP, Banerjee S, Ghosh LM, et al. Benign pleomorphic adenoma of the larynx. Report of a cases and review and analysis of 20 additional cases in the literature. *Ear Nose Throat J* 1997; 76:548-557.
5. MacMillan RH III, Fechner RE. Pleomorphic adenoma of the larynx. *Arch Pathol Lab Med* 1986; 110:245-247.
6. Sabri JA, Hajjar A. Malignant mixed tumor of the vocal cord. Report of a case. *Arch Otolaryngol* 1967; 85:332-334.
7. Bomer DL, Arnold GE. Malignant mixed tumors of the minor salivary glands. *Acta Otolaryngol* 1971; suppl 289.
8. Milford CA, Mugliston TA, O'Flynn P, et al. Carcinoma arising in a pleomorphic adenoma of the epiglottis. *J Laryngol Otol* 1989; 103:324-327.
9. Myers JN, Myers EN, Barnes EL. Benign neoplasms of the larynx in *The Larynx. A Multidisciplinary Approach*, 2nd ed, Fried MP, editor, Mosby, St. Louis, 1996:443-459.
10. Gallagher JC, Puzon BQ. Oncocytic lesions of the larynx. *Ann Otol Rhinol Laryngol* 1969; 78:307-317.
11. Olofsson J, van Nostrand AWP. Adenoid cystic carcinoma of the larynx. A report of four cases and a review of the literature. *Cancer* 1955; 40:1307-1313.
12. Ferlito A, Caruso G. Biological behavior of laryngeal adenoid cystic carcinoma. Therapeutic considerations. *ORL* 1983; 45:245-256.
13. Tewfik TL, Novick WH, Schipper HM. Adenoid cystic carcinoma of the larynx. *J Otolaryngol* 1983; 12:151-154.
14. Donovan DT, Conley J. Adenoid cystic carcinoma of the subglottic region. *Ann Otol Rhinol Laryngol* 1983; 92: 491-495.
15. Stillwagon GB, Smith RRL, Highstein C, et al. Adenoid cystic carcinoma of the supraglottic larynx: report of a case and review of the literature. *Am J Otolaryngol* 1985; 6:309-314.
16. Ferlito A, Barnes L, Myers EN. Neck dissection for laryngeal adenoid cystic carcinoma: is it indicated? *Ann Otol Rhinol Laryngol* 1990; 99:277-280.
17. Shin YJ, Percodani J, Corte EU, et al. Adenoid cystic carcinoma of the larynx. A case report and review of the literature. *Rev Laryngol Otol Rhinol (Bord)* 1998; 119:105-108.
18. Damborenea TJ, Campos del Alamo MA, Marin GL, et al. Adenoid cystic carcinoma of the larynx. Case report and literature review. *An Otorhinolaryngol Ibero Am* 1999; 26:257-263.
19. Yang PY, Liu MS, Chen CH, et al. Adenoid cystic carcinoma of the trachea: a report of seven cases and literature review. *Chang Gung Med J* 2005; 28:357-363.
20. Spiro RH, Huvoos AG, Strong EW. Adenoid cystic carcinoma: factors influencing survival. *Am J Surg* 1979; 138:579-583.
21. El-Jabbour JN, Ferlito A, Friedman I. Salivary gland neoplasms. In: *Neoplasms of the Larynx*. (Ferlito A, ed). Edinburgh: Churchill-Livingstone, 1993:231-264.
22. Damiani JM, Damiani KK, Hauck K, et al. Mucoepidermoid-adenosquamous carcinoma of the larynx and hypopharynx: a report of 21 cases and review of the literature. *Otolaryngol Head Neck Surg* 1981; 89:235-243.
23. Prgomet D, Bilic M, Bumber Z, et al. Mucoepidermoid carcinoma of the larynx: report of three cases. *J. Laryngol Otol* 2003; 117:998-1000.

24. Boscolo-Rizzo P, da Mosto MC, Marchiori C, et al. Transglottic acinic cell carcinoma. Case report and literature review. *ORL* 2004; 66:286–289.
25. Pesavento G, Ferlito A, Reher G. Primary clear cell carcinoma of the larynx. *J Clin Pathol* 1980; 33:1160–1164.
26. Seo IS, Tomich CE, Warfel KA, et al. Clear cell carcinoma of the larynx. A variant of mucoepidermoid carcinoma. *Ann Otol Rhinol Laryngol* 1980; 89:168–172.
27. Batsakis JG, Hyams VJ, Morales AR. Special tumors of the head and neck. Proceedings of the Forty-eighth Annual Seminar of American Society of Clinical Pathologists. Chicago: American Society of Clinical Pathologists' Press, 1983.
28. Ibrahim R, Bird DJ, Sieler MW. Malignant myoepithelioma of the larynx with massive metastatic spread to the liver: an ultra-structural and immunocytochemical study. *Ultrastruct Pathol* 1991; 15:69–76.
29. Mikaelian DO, Contrucci RB, Batsakis JG. Epithelial-myoepithelial carcinoma of the subglottic region. A case presentation and review of the literature. *Otolaryngol Head Neck Surg* 1986; 95:104–106.
30. Goel MM, Agrawal SP, Srivastava AN. Salivary duct carcinoma of the larynx: report of a rare case. *Ear Nose Throat J* 2003; 82:371–373.
31. Ferlito A, Gale N, Hvala A. Laryngeal salivary duct carcinoma. A light and electron microscopic study. *J Laryngol Otol* 1981; 95:731–738.
32. Robinson AC, Kaberos A, Cox PM, et al. Oncocytoma of the larynx. *J Laryngol Otol* 1990; 104:346–349.
33. Johns ME, Batsakis JG, Short CD. Oncocytic and oncocytoid tumors of the salivary glands. *Laryngoscope* 1973; 83:1940–1952.
34. Roa RA, Atkins JP Jr., Cunnane MF, et al. Papillary adenocarcinoma of the larynx: a case report. *Otolaryngol Head Neck Surg* 1988; 99:601–603.
35. Tsang YW, Ngan KC, Chan JKC. Primary mucoid adenocarcinoma of the larynx. *J Laryngol Otol* 1991; 105:315–317.

XXV. MELANOTIC LESIONS OF THE LARYNX

1. Har-El G, Borederon M, Ladinsky S, et al. Melanosis of the larynx. *Ann Otol Rhinol Laryngol* 1990; 99:640–642.
2. Goldman JL, Lawson W, Zak FG, et al. The presence of melanocytes in the human larynx. *Laryngoscope* 1972; 82:824–835.
3. Busuttil A. Dendritic pigmented cells within human laryngeal mucosa. *Arch Otolaryngol* 1976; 102:43–44.
4. Gonzalez-Vela MC, Fernandez FA, Mayorga M, et al. Laryngeal melanosis: Report of four cases and literature review. *Otolaryngol Head Neck Surg* 1997; 117:708–712.
5. Reuter VE, Woodruff JM. Melanoma of the larynx. *Laryngoscope* 1986; 94:389–393.
6. Wenig BM. Laryngeal mucosal malignant melanoma. A clinicopathologic, immunohistochemical, and ultrastructural study of four patients and a review of the literature. *Cancer* 1995; 75:1568–1577.
7. Seals JL, Shenefelt RE, Babin RW. Intralaryngeal nevus in a child. A case report. *Int J Pediatr Otorhinolaryngol* 1986; 12:55–58.
8. Schimpf A, Musebaeck K, Mootz W. Naevuszellnaevus (compoundnaevus) im Larynxbereich (plica ventricularis). *Z Haut Geschlechtskr* 1969; 44:137–144.
9. Wenig BM. Malignant melanoma. In: Neoplasms of the larynx. (Ferlito A, ed). Edinburgh: Churchill Livingstone, 1993:207–230.
10. Travis LW, Sutherland C. Coexisting lentigo of the larynx and melanoma of the oral cavity: report of a case. *Otolaryngol Head Neck Surg* 1980; 88:218–220.

11. Amin HM, Petruzzelli GJ, Husain AN, et al. Primary malignant melanoma of the larynx. *Arch Pathol Lab Med* 2001; 125:271–273.
12. Batsakis JG, Luna MA, Byers RM: Metastases to the larynx. *Head Neck Surg* 1985; 7:458–460.
13. Ferlito A, Caruso G, Reher G. Secondary laryngeal tumors. Report of seven cases with review of the literature. *Arch Otolaryngol Head Neck Surg* 1988; 114: 635–639.
14. Patel JK, Didolkar MS, Pickren JW, et al. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. *Am J Surg* 1978; 135:807–810.
15. Henderson LT, Robbins T, Weitzner S. Upper aerodigestive tract metastases in disseminated malignant melanoma. *Arch Otolaryngol Head Neck Surg* 1986; 112:659–663.
16. Pau H, Spencer MG, Steele PRM. Metastatic malignant melanoma of the larynx. *J Laryngol Otol* 2001; 115:925–927.

XXVI. GIANT CELL TUMOR

1. Wieneke JA, Gannon FH, Heffner DK, et al. Giant cell tumor of the larynx: A clinicopathologic series of eight cases and a review of the literature. *Mod Pathol* 2001; 14:1209–1215.
2. Devaney KO, Ferlito A, Rinaldo A. Giant cell tumor of the larynx. *Ann Otol Rhinol Laryngol* 1998; 107:729–732.
3. Hall-Jones J. Giant cell tumour of the larynx. *J Laryngol Otol* 1972; 86:371–381.
4. Hinni ML. Giant cell tumour of the larynx. *J Laryngol Otol* 1972; 86:371–381.
5. Martin PC, Hoda SA, Pigman HT, et al. Giant cell tumor of the larynx. Case report and review of the literature. *Arch Pathol Lab Med* 1994; 118:834–837.
6. Ribari O, Elemr G, Balint A. Laryngeal giant cell tumour. *J Laryngol Otol* 1975; 89:857–861.
7. Thomas DM, Wilkins MJ, Witana JS, et al. Giant cell reparative granuloma of the cricoid cartilage. *J Laryngol Otol* 1995; 109:1120–1123.

XXVII. INFLAMMATORY MYOFIBROBLASTIC TUMOR

1. Coffin CM, Fletcher JA. Inflammatory myofibroblastic tumor in World Health Organization Classification of Tumours, Pathology and Genetics, Tumours of Soft Tissue and Bone, Fletcher, CDM, Unni KK, Martens F, editors, Lyon, IARC Press, 2002:91–93.
2. Gomez-Roman JJ, Ocejio-Vinyals G, Sanchez-Velasco P, et al. Presence of human herpes virus 8 DNA sequences and overexpression of human IL-6 and cyclin D1 in inflammatory myofibroblastic tumor (inflammatory pseudotumor). *Lab Invest* 2000; 80:1121–1126.
3. Cheuk W, Chan JKC, Shek TWH, et al. Inflammatory pseudotumor-like follicular dendritic cell tumor. A distinctive low-grade malignant intra-abdominal neoplasm with consistent Epstein-Barr virus association. *Am J Surg Pathol* 2001; 25:721–731.
4. Kazmierczak B, Cin PD, Sciort R, et al. Inflammatory myofibroblastic tumor with HMGIC rearrangement. *Cancer Genet Cytogenet* 1999; 112:156–160.
5. Su LD, Atayde-Perez A, Sheldon S, et al. Inflammatory myofibroblastic tumor: Cytogenic evidence supporting clonal origin. *Mod Pathol* 1998; 11:364–368.
6. Hussong JW, Brown M, Perkins SL, et al. Comparison of DNA ploidy, histologic, and immunohistochemical findings with clinical outcomes in inflammatory myofibroblastic tumors. *Mod Pathol* 1999; 12:279–286.

7. Cook JR, Dehner LP, Collins MH, et al. Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor. A comparative immunohistochemical study. *Am J Surg Pathol* 2001; 25:1364–1371.
8. Coffin CM, Patel A, Perkins S, et al. ALK 1 and p80 expression and chromosomal rearrangement involving 2p23 in inflammatory myofibroblastic tumors. *Mod Pathol* 2001; 14:569–576.
9. Som PM, Brandwein MS, Maldjian C, et al. Inflammatory pseudotumor of the maxillary sinus: CT and MR findings in six cases. *AJR* 1994; 163:689–692.
10. Benton NC, Korol HW, Smyth LT Jr. Plasma cell granuloma of the middle ear and mastoid. Case report. *Ann Otol Rhinol Laryngol* 1992; 101:92–94.
11. Mulder JJS, Cremers WR, Joosten F, et al. Fibroinflammatory pseudotumor of the ear. A locally destructive benign lesion. *Arch Otolaryngol Head Neck Surg* 1995; 121:930–933.
12. Perez M, Barnes L. Inflammatory (myofibroblastic) pseudotumors (IPT) of the head and neck. *Mod Pathol* 1999; 12:129A (abstract).
13. Wenig BM, Devaney K, Bisceglia M. Inflammatory myofibroblastic tumor of the larynx. A clinicopathologic study of eight cases simulating a malignant spindle cells neoplasm. *Cancer* 1995; 76:2217–2229.
14. Hytiroglou P, Brandwein MS, Strauchen JA, et al. Inflammatory pseudotumor of the parapharyngeal space: Case report and review of the literature. *Head Neck* 1992; 14:230–234.
15. Inui M, Tagawa T, Mori A, et al. Inflammatory pseudotumor in the submandibular region. Clinicopathologic study and review of the literature. *Oral Surg Oral Med Oral Pathol* 1993; 76:333–337.
16. Williams SB, Foss RD, Ellis GL. Inflammatory pseudotumors of the major salivary glands. Clinicopathologic and immunohistochemical analysis of six cases. *Am J Surg Pathol* 1992; 16:896–902.
17. Martinez S, Bosch R, Pardo J, et al. Inflammatory myofibroblastic tumour of the larynx. *J Laryngol Otol* 2001; 115:140–142.
18. Munoz A, Villafruela M. Inflammatory pseudotumor of the larynx: MR findings in a child. *Pediatr Radiol* 2001; 31:459–460.
19. Rodriguez M, Taylor RJ, Sun CC, et al. Inflammatory myofibroblastic tumor of the larynx in a 2-year-old male. *ORL J Otorhinolaryngol Relat Spec* 2005; 67:101–105.
20. Suh S, Seol HY, Lee JH, et al. Inflammatory myofibroblastic tumor of the larynx. *Head Neck* 2006; 28:369–372.
21. Guilemany JM, Alos L, Alobid I, et al. Inflammatory myofibroblastic tumor in the larynx: Clinicopathologic features and histogenesis. *Acta Oto-Laryngologica* 2005; 125:215–219.
22. Coffin CM, Humphrey PA, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor: A clinical and pathological study. *Semin Diagn Pathol* 1998; 15:85–101.
23. Coffin CM, Dehner LP, Meis-Kindblom JM. Inflammatory myofibroblastic tumor, inflammatory fibrosarcoma and related lesions. An historical review with differential diagnostic considerations. *Semin Diagn Pathol* 1998; 15:102–110.
3. Prasad JN. Fibrosarcoma of the larynx. *J Laryngol Otol* 1972; 86:267–273.
4. Coia LR, Frazekas JT, Kramer S. Post-Irradiation sarcoma of the head and neck: a report of three late sarcomas following therapeutic irradiation for primary malignancies of the paranasal sinus, nasal cavity, and larynx. *Cancer* 1980; 46:1982–1985.
5. Kim JH, Chu FC, Woodward HQ, et al. Radiation-induced soft tissue and bone sarcoma. *Radiology* 1978; 129:501–508.
6. Setzen M, Sobol S, Toomey JM. Clinical course of unusual malignant sarcomas of the head and neck. *Ann Otol Rhinol Laryngol* 1979; 88:486–494.
7. Brockstein B. Management of sarcomas of the head and neck. *Curr Oncol Rep* 2004; 6:321–327.
8. Barnes L. Tumors and tumorlike lesions of the soft tissues. In: *Surgical Pathology of the Head and Neck* (Barnes L, ed). New York: Marcel Dekker, 1985:725–880.

XXIX. SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX

XXVIII. SARCOMAS OF THE LARYNX

1. Cady B, Ripey JH, Frazell EL. Non-epidermoid cancer of the larynx. *Ann Surg* 1968; 167:116–120.
2. Kraina Z. Laryngeal sarcoma. In: *Centennial Conference on Laryngeal Carcinoma*. (PW Alberti, DP Bryce, eds). New York: Appleton-Century-Crofts, 1976:485–488.
1. Lefebvre JL, Castelain B, De La Torre JC, et al. Lymph node invasion in hypopharynx and lateral epilynx carcinoma: a prognostic factor. *Head Neck Surg* 1987; 10:14–18.
2. Hasegawa Y, Matsuura H. Retropharyngeal node dissection in cancer of the oropharynx and hypopharynx. *Head Neck* 1994; 16:173–180.
3. Olofsson J, van Nostrand AWP. Growth and spread of laryngeal and hypopharyngeal carcinoma with reflections on the effect of preoperative irradiation: 139 cases studied by whole organ serial sectioning. *Acta Otolaryngol Suppl* 1973; 308:1–84.
4. Bryce D. The conventional surgical management of carcinoma of the hypopharynx. *J Laryngol Otol* 1971; 85:1221–1226.
5. Shah JP, Shaha AR, Spiro RH, et al. Carcinoma of the hypopharynx. *Am J Surg* 1976; 132:439–443.
6. Stefani S, Eells RW. Carcinoma of the hypopharynx—a study of distant metastases, treatment failures, and multiple primary cancers in 215 male patients. *Laryngoscope* 1971; 81:1491–1498.
7. Kirchner JA. Pyriform sinus cancer: a clinical and laboratory study. *Ann Otol Rhinol Laryngol* 1975; 84:793–803.
8. Razack MS, Sako K, Marchetta FC, et al. Carcinoma of the hypopharynx: success and failure. *Am J Surg* 1977; 134:489–491.
9. ElBadawi Sa, Goepfert H, Fletcher GH, et al. Squamous cell carcinoma of the pyriform sinus. *Laryngoscope* 1982; 92:357–364.
10. Keane TJ. Carcinoma of the hypopharynx. *J Otolaryngol* 1982; 11:227–231.
11. Barnes L, Johnson JT. Pathologic and clinical considerations in the evaluation of major head and neck specimens resected for cancer. *Pathol Annu (Part 1)* 1986; 21:173–250.
12. Vogler WR, Lloyd JW, Milmore BK. A retrospective study of etiological factors in cancer of the mouth, pharynx and larynx. *Cancer* 1962; 15:246–258.
13. Keller AZ. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. *Cancer* 1967; 20:1015–1022.
14. Wynder EL, Hultberg S, Jacobsson F, et al. Environmental factors in cancer of the upper alimentary tract. A Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. *Cancer* 1957; 10:470–487.
15. Goldstein F. Dysphagia with iron deficiency (Plummer-Vinson syndrome, Paterson Brown syndrome, sideropenic dysphagia). In: *Gastroenterology*, 3rd ed. (Bockus HL, ed), Philadelphia: WB Saunders, 1974:339–343.

16. Carpenter RJ III, DeSanto LW, Devine KD, et al. Cancer of the hypopharynx. Analysis of treatment and results in 162 patients. *Arch Otolaryngol* 1976; 102:716–721.
17. Shimakage M, Sasagawa T, Yoshino K, et al. Expression of Epstein-Barr virus in mesopharyngeal and hypopharyngeal carcinomas. *Hum Pathol* 1999; 30:1071–1076.
18. Cunningham MP, Catlin D. Cancer of the pharyngeal wall. *Cancer* 1967; 20:1859–1866.
19. Inoue T, Shigematsu Y, Sato T. Treatment of carcinoma of the hypopharynx. *Cancer* 1973; 31:649–655.
20. Jorgensen K. Carcinoma of the hypopharynx: therapeutic results in a series of 103 patients. *Acta Radiol* 1971; 10: 465–473.
21. Farrington WT, Weighill JS, Jones PH. Post-cricoid carcinoma (a ten-year retrospective study). *J Laryngol Otol* 1986; 100:79–86.
22. Harrison DFN. Malignant disease of the hypopharynx. Surgical pathology of hypopharyngeal neoplasms. *J Laryngol Otol* 1971; 85:1215–1218.
23. Horwitz SD, Caldarelli DD, Hendrickson FR. Treatment of carcinoma of the hypopharynx. *Head Neck Surg* 1979; 2:107–111.
24. AJC Cancer Staging Manual, 6th ed, Greene FL, Page DL, Fleming ID, et al, editors, New York, Springer, 2002:33–45.
25. McGavran MH, Bauer WC, Spjut HJ, et al. Carcinoma of the pyriform sinus. The results of radical surgery. *Arch Otolaryngol* 1963; 78:826–830.
26. Eibach KJ, Krause CJ. Carcinoma of the pyriform sinus. A comparison of treatment modalities. *Laryngoscope* 1977; 87:1904–1910.
27. Smith RR, Frazell EL, Chaulk R, et al. The American Joint Committee's proposed method of stage classification and end results reporting applied to 1320 pharyngeal cancers. *Cancer* 1963; 16:1505–1520.
28. Wilkins SA Jr. Carcinoma of the posterior pharyngeal wall. *Am J Surg* 1971; 122:477–481.
29. Wang CC. Radiotherapeutic management of carcinoma of the posterior pharyngeal wall. *Cancer* 1971; 27:894–896.
30. Ballantyne AJ. Principals of surgical management of cancer of the pharyngeal wall. *Cancer* 1967; 20:663–667.
31. McNab Jones RF. The Paterson-Brown-Kelly syndrome. Its relationship to iron deficiency and postcricoid carcinoma. *J Laryngol Otol* 1961; 75:529–561.
32. Richards SH, Kilby D, Shaw JD. Post-cricoid carcinoma and Paterson-Kelly syndrome. *J Laryngol Otol* 1971; 85: 141–152.
33. Harrison DFN. Thyroid gland in the management of laryngopharyngeal carcinoma. *Arch Otolaryngol* 1973; 97:301–302.
34. Harrison DFN. Surgical management of cancer of the hypopharynx and cervical esophagus. *Br J Surg* 1969; 56: 95–103.
35. Harrison DFN. Pathology of hypopharyngeal cancer in relation to surgical management. *J Laryngol Otol* 1970; 84: 349–367.
36. DeSanto LW, Carpenter RJ. Reconstruction of the pharynx and upper esophagus after resection for cancer. *Head Neck Surg* 1980; 2:369–379.
37. Harwick RD. Carcinoma of the pyriform sinus. *Am J Surg* 1975; 130:493–495.
38. Lederman M. Cancer of the pharynx: a study based on 2417 cases with special reference to radiation treatment. *J Laryngol Otol* 1967; 81:151–172.
39. Jesse RH, Lindberg RD. The efficiency of combining radiation therapy with a surgical procedure in patients with cervical metastasis from squamous cell cancer of the oropharynx and hypopharynx. *Cancer* 1975; 35:1163–1166.
40. Marchetta FC, Sako K, Holyoke ED. Squamous cell carcinoma of the pyriform sinus. *Am J Surg* 1967; 114:507–509.
41. Marks JE, Kurnik B, Powers WE, et al. Carcinoma of the pyriform sinus: an analysis of treatment results and patterns of failure. *Cancer* 1978; 41:1008–1015.
42. Razack MS, Sako K, Kalnins I. Squamous cell carcinoma of the pyriform sinus. *Head Neck Surg* 1978; 1:31–34.
43. McNeill R. Surgical management of carcinoma of the posterior pharyngeal wall. *Head Neck Surg* 1981; 3:389–394.
44. Marks JE, Smith PG, Sessions DG. Pharyngeal wall cancer. A reappraisal after comparison of treatment methods. *Arch Otolaryngol* 1985; 111:79–85.
45. Teichgraber JF, McConnel FMS. Treatment of posterior pharyngeal wall carcinoma. *Otolaryngol Head Neck Surg* 1986; 94:287–290.
46. Spiro RH, Kelly J, Vega AL, et al. Squamous carcinoma of the posterior pharyngeal wall. *Am J Surg* 1990; 160:420–423.
47. Sasaki CT, Salzer SJ, Cahow E, et al. Laryngopharyngoesophagectomy for advanced hypopharyngeal and esophageal squamous cell carcinoma: the Yale experience. *Laryngoscope* 1995; 105:160–163.
48. Barzan L, Barra S, Franchin G, et al. Squamous cell carcinoma of the posterior pharyngeal wall: characteristics compared with the lateral wall. *J Laryngol Otol* 1995; 109:120–125.
49. Vandenbrouck C, Sancho H, LeFur R, et al. Results of a randomized clinical trial of preoperative irradiation versus postoperative in treatment of tumors of the hypopharynx. *Cancer* 1977; 39:1445–1449.
50. Vandenbrouck C, Eschwege F, De La Rochefordiere A, et al. Squamous cell carcinoma of the pyriform sinus: retrospective study of 351 cases treated at the Institut Gustave-Roussy. *Head Neck Surg* 1987; 10:4–13.
51. Pingree TF, Davis RK, Reichman O, et al. Treatment of hypopharyngeal carcinoma: a 10-year review of 1,362 cases. *Laryngoscope* 1987; 97:901–904.
52. Jones AS, Wilde A, McRae RD, et al. The treatment of early squamous cell carcinoma of the pyriform fossa. *Clin Otolaryngol* 1994; 19:485–490.
53. Harrison DFN, Thompson AE. Pharyngolaryngoesophagectomy with pharyngeogastric anastomosis for cancer of the hypopharynx: review of 101 operations. *Head Neck Surg* 1986; 8:418–428.
54. Sasaki TM, Baker HW, Yeager RA, et al. Aggressive surgical management of pyriform sinus carcinoma. A 15 year experience. *Am J Surg* 1986; 151:590–592.
55. Bataini JP, Bernier J, Jaulerry C, et al. Impact of cervical disease and its definitive radiotherapeutic management on survival: experience in 2013 patients with squamous cell carcinomas of the oropharynx and pharyngolarynx. *Laryngoscope* 1990; 100:716–723.
56. Spector JG, Sessions G, Emami B, et al. Squamous cell carcinoma of the pyriform sinus: a nonrandomized comparison of therapeutic modalities and long-term results. *Laryngoscope* 1995; 105:397–406.

XXX. TUMORS OF THE TRACHEA

1. Maziak DE, Todd TRJ, Keshavjee SH, et al. Adenoid cystic carcinoma of the airway: Thirty-two-year experience. *J Thorac Cardiovasc Surg* 1996; 112:1522–1532.
2. Gilbert JG, Kaufman B, Mazzanella LA. Tracheal tumors in infants and children. *J Pediatr* 1949; 35:63–69.
3. Desai DP, Holinger LD, Gonzalez-Crussi F. Tracheal neoplasms in children. *Ann Otol Rhinol Laryngol* 1998; 107:790–796.
4. Grillo HC, Mathisen DJ. Primary tracheal tumors: Treatment and results. *Ann Thorac Surg* 1990; 49:69–77.
5. Eschappasse H. Les tumeurs tracheales primitives traitement chirurgical. *Rev Fr Mal Resp* 1974; 2:425–446.

6. Gelder CM, Hetzel MR. Primary tracheal tumours: a national survey. *Thorax* 1993; 48:688-692.
7. Manninen MP. Symptoms and signs and their prognostic value in tracheal carcinoma. *Eur Arch Otorhinolaryngol* 1993; 250:383-386.
8. Grillo HC, Dignan EF, Miura T. Extensive resection and reconstruction of mediastinal trachea without prosthesis or graft: An anatomical study. *J Thorac Cardiovasc Surg* 1964; 48:741-749.
9. Mathisen DJ, Grillo HC. Tumors of the cervical trachea. In: *Cancer of the Head and Neck*, 3rd edition, Myers EN, Suen JY, eds. WB Saunders, Philadelphia: 1996:439-461.
10. Anson BJ. Morris' Human Anatomy, 12 edition, McGraw Hill New York: 1966; 1430.
11. Webb BD, Walsh GL, Roberts DE, et al. Primary tracheal malignant neoplasms: the University of Texas MD Anderson Cancer Center experience. *J Am Coll Surg* 2006; 202:237-246.
12. Fields JN, Rigard G, Emani BN. Primary tumors of the trachea. Results of radiation therapy. *Cancer* 1989; 63:2429-2433.
13. Howard DJ. Primary tumours of the trachea: analysis of clinical features and treatment results. *J Laryngol Otol* 1994; 108:230-232.
14. Rafely Y, Weissberg D. Surgical management of tracheal tumors. *Ann Thorac Surg* 1997; 64:1429-1433.
15. Schneider P, Schirren J, Muley T, et al. Primary tracheal tumors: experience with 14 resected patients. *Eur J Cardio-Thorac Surg* 2001; 20:12-18.
16. Chow DC, Komaki R, Libshitz HI, et al. Treatment of primary neoplasms of the trachea. The role of radiation therapy. *Cancer* 1993; 71:2946-2952.

XXXI. METASTASES TO THE LARYNX, HYPOPHARYNX AND TRACHEA

1. Batsakis JG, Luna MA, Byers RM. Metastases to the larynx. *Head Neck Surg* 1985; 7:458-460.
2. Ferlito A. Secondary neoplasms. In: *Neoplasms of the Larynx*, Ferlito A, ed. Edinburgh: Churchill Livingstone, 1993:349-360.
3. Ferlito A, Caruso G, Recher G. Secondary laryngeal tumors. Report of seven cases with review of the literature. *Arch Otolaryngol Head Neck Surg* 1988; 114: 635-639.
4. Baumgartner WA, Mark JB. Metastatic malignancies from distant sites to the tracheobronchial tree. *J Thorac Cardiovasc Surg* 1980; 79:499-503.
5. Westerman DE, Urbanetti JS, Rudders RA, et al. Metastatic endotracheal tumor from ovarian carcinoma. *Chest* 1980; 77:798-800.
6. Mackenzie IJ, Morgan JM, Mitchell JF. Secondary tracheal carcinoma. *J Laryngol Otol* 1981; 95:973-978.
7. Nicolai P, Peretti G, Cappiello J, et al. Melanoma metastatic to the trachea and nasal cavity: description of a case and review of the literature. *Acta Otorhinolaryngol Ital* 1991; 11:85-92.
8. Conti JA, Kemeny N, Klimstra D, et al. Colon carcinoma metastatic to the trachea. Report of a case and review of the literature. *Am J Clin Oncol* 1994; 17:227-229.
9. Koyi H, Branden E. Intratracheal metastasis from malignant melanoma. *J Eur Acad Dermatol Venereol* 2000; 14:407-408.

Benign and Nonneoplastic Diseases of the Oral Cavity and Oropharynx

Robert A. Robinson

*Department of Pathology, The University of Iowa, Roy J. and Lucille A. Carver
College of Medicine, Iowa City, Iowa, U.S.A.*

Steven D. Vincent

*Department of Oral Pathology, Oral Radiology and Oral Medicine, The University of Iowa
College of Dentistry, Iowa City, Iowa, U.S.A.*

I. FORDYCE GRANULES

Fordyce granules are developmental anomalies of the oral mucosa. They are thought to arise from ectoderm inclusions formed during the fusion of the mandibular and maxillary processes. Fordyce granules, also known as Fordyce spots, are extremely common. There is an increasing frequency of Fordyce granules with age up to the second and third decades, with males exhibiting the process earlier and more frequently than females in childhood. While unusual in infants, Fordyce granules is found to be present in approximately 60% of children 10 years and younger, and close to 90% of adults are reported to show these lesions (1–3). Although proposed by Fordyce originally to be the result of the degeneration of the prickle cells of the oral epithelium, these lesions are ectopic sebaceous glands. The most common sites include the buccal mucosa and vermilion borders of the lips. Other extra head and neck mucosal sites include the esophagus, uterine cervix, and thyroglossal duct (4). They are not found in the conjunctiva, but have been reported in patients that have undergone oral mucous membrane grafts to correct inflammatory processes (5,6).

A. Clinical Features

Fordyce granules are asymptomatic and appear as groups of small yellowish, submucosal globoid lesions forming large plaques or small, separate foci. They are often bilateral and symmetric on the buccal mucosa opposite the mandibular first molars and are also common in the retromolar mucosa lateral to the anterior pillars of the fauces (Fig. 1). They may also be seen on the hard and soft palate, tongue, floor of the mouth, alveolar ridge, and frenulum. The granules are sometimes slightly elevated and range from 1 to 2 mm in diameter. They may be widely separated or clustered and may coalesce into plaque-like lesions measuring 1 cm or more.

B. Pathology

Histologically, normal-appearing sebaceous glands are seen directly beneath the epithelium and may have a central duct (Fig. 2). Generally these ducts do not open to the surface. The only difference between Fordyce granules and sebaceous units of the skin is that they lack associated hair follicles. Rarely Fordyce granules have been reported to actively secrete (7). Very rarely Fordyce granules have been associated with sebaceous adenomas, keratin-filled cysts, and steatocystoma simplex (8). Sebaceous carcinoma of the oral mucosa has been reported, but its direct association with Fordyce granules is difficult to confirm (9).

C. Treatment and Prognosis

Fordyce granules do not require treatment (10). Some lesions have been treated with isotretinoin (11).

II. WHITE SPONGE NEVUS

White sponge nevus is a rare benign autosomal dominant disorder of the mucus membranes that results in disordered epithelial differentiation. It is not a melanocytic lesion but considered a hereditary leukokeratosis. Its first description is generally attributed to Cannon in 1935 (1–4). Synonyms include pachyderma oralis, hereditary leukokeratosis, familial white folded dysplasia of the mucous membrane, congenital leukokeratosis mucosa oris, and oral epithelial nevus. White sponge nevus has been reported in the mucosa of the nose, esophagus, rectum, anus, vagina, as well as the mucosa of the oral cavity (5–8).

A. Clinical Features

White sponge nevus is asymptomatic. As it is inherited, the appearance of white sponge nevus in



Figure 1 Fordyce granule. Fordyce granules (ectopic sebaceous glands) of oral mucosa appear clinically as 1 to 2 mm diameter, yellow submucosal nodules. They can be single or in groups. They are most often identified in the mucosa of the lips and buccal mucosa.

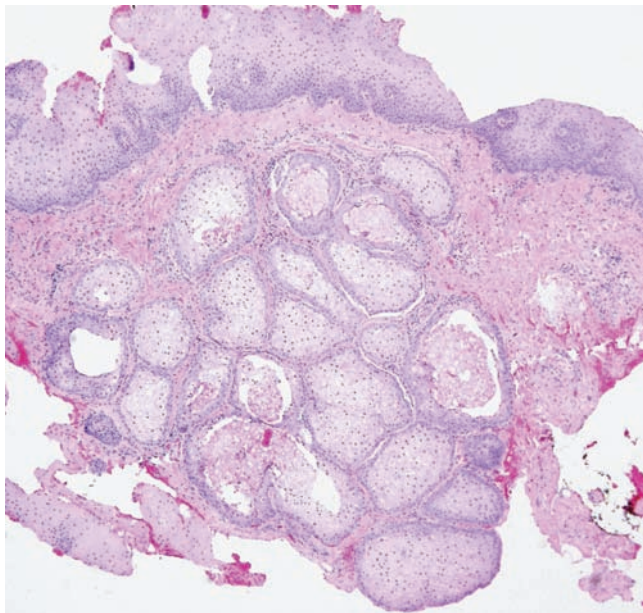


Figure 2 Fordyce granule. Clusters of acini and ducts characteristic of typical sebaceous glands. Cytoplasm of secretory cells is usually clear or foamy with centrally placed nuclei.

childhood is not unexpected, and it may be identified at birth. Bilateral involvement of the buccal mucosa is most common but other sites include the lips, palate, ventral tongue, peritonsillar, and hypopharyngeal



Figure 3 White sponge nevus. Diffuse, white, wrinkled areas involve widespread areas of oral mucosa, including buccal, labial, glossal, gingival, and palatal mucosa.

areas. The process appears as spongy and white plaques with a folded appearance; hence the synonym familial white folded dysplasia of the mucus membrane (6) (Fig. 3). The lesions may be single or multiple.

B. Pathology

The histologic features of the white sponge nevus are typified by acanthotic epithelium with parakeratosis (Fig. 4). Keratin aggregates, characteristic of the lesion, are present in the suprabasal cells. Intracellular edema is seen by light and electron microscopy, with hyperkeratotic plugs extending deep into the acanthotic layers. These hyperkeratotic plugs are useful for the histologic diagnosis and are considered pathognomonic (9).

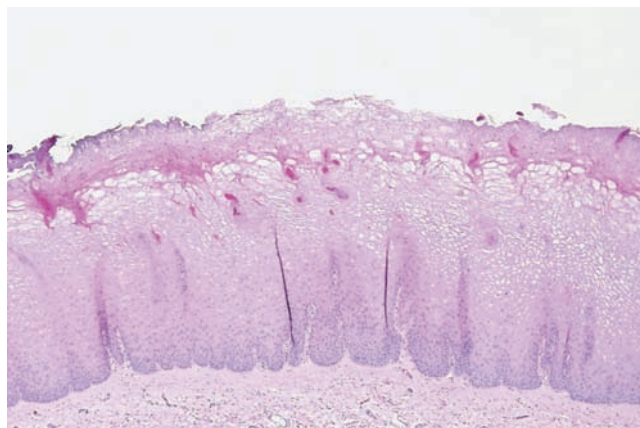


Figure 4 White sponge nevus. The epithelium shows relatively uniform acanthosis, spongiosis, and hyperparakeratosis. There should be no evidence of dysplasia.

C. Molecular and Genetic Data

White sponge nevus is an autosomal dominant process with high penetrance. Many genetic conditions affecting squamous epithelium, either skin or mucosa, are due to mutations in keratin genes. Keratins have a common structure of a central helical rod domain flanked by nonhelical head and tail domains (4,12). Helix boundary peptides begin and end the central rod domain and are common sites for keratin mutations. Recent studies have found mutations in keratins K4 and K13 genes, which encode mucosa-specific keratins (10–13). Mutations in these regions, such as seen in white sponge nevus, are associated with conditions in which there is keratin filament aggregation. Mutations in the helix initiation peptide of K4 and K13 in affected members from two families have been reported (11,12).

D. Differential diagnosis

The clinical differential can include chronic cheek biting, although these lesions should be localized to the buccal and glossal mucosa directly adjacent to the teeth. Other genodermatoses may mimic white sponge nevus, including keratosis follicularis, pachonychia congenita, hereditary benign intraepithelial dyskeratosis, and ichthyosiform dermatoses. Atypical squamous diseases such as proliferative verrucous leukoplakia can also mimic white sponge nevus, although the clinical features and historical data of time of onset of the lesions are usually helpful in determining if a biopsy is indicated.

E. Treatment and Prognosis

The lesions require no treatment. White sponge nevus has not been shown to be premalignant.

III. ORAL MELANOCYTIC NEVI

Oral melanocytic nevi are known by a variety of other names, including mole, pigmented nevus, and nevo-cellular nevus. Oral melanocytic nevi are uncommon in the oral mucosa, but solitary oral pigmented lesions of melanocytic origin as a whole are uncommon. In a study of 89,430 biopsies accessioned in an oral and maxillofacial pathology laboratory during a 19-year period, 773 (0.83%) were solitary pigmented melanocytic lesions (1). Oral melanotic macules comprised 86.1% of the melanocytic group (0.7% of the entire accessioned biopsy series), and oral melanocytic nevi comprised 11.8% (0.1% of the entire accessioned biopsy series). For comparison, melanomas and atypical melanocytic proliferations comprised just 0.6% of the melanocytic group and 0.006% of the total accessioned biopsies in the series. The very infrequent development of intraoral mucosal nevi contrasts sharply with the ubiquitous nature of cutaneous melanocytic nevi seen in individuals with light skin.

A. Clinical Features

Most intraoral nevi are less than 1 cm and the majority are 0.1 to 0.3 cm (2). Congenital oral melanocytic nevi are extremely rare (3). The highest incidence appears to be in the third and fourth decades. In contrast to nevi occurring in the skin, where there is no gender predominance, oral mucosal nevi are more common in females. The most common site of oral melanocytic nevi is the palate. Interestingly, the palate is also the most common site for the very rare occurrence of intraoral melanoma. Other sites of involvement by oral melanocytic nevi include the buccal mucosa, the gingiva, vermillion border of the lip, soft palate, and retromolar trigone. Unusual sites include the tongue and floor of the mouth. Oral melanocytic nevi usually have distinct borders but may be flat, elevated, or exophytic.

As in the skin, melanocytic nevi occur in the oral mucosa as intraepithelial (junctional), compound, or intramucosal lesions. Intramucosal lesions are by far the most common variety; however, all the types of melanocytic nevi of the skin may be seen as counterparts in the oral mucosa, including balloon cell nevus, common blue nevus, and cellular blue nevus (2,4–6). In descending order of frequency the types are intramucosal, compound, and common blue nevus, with junctional nevus being the least common of this group. Combined nevi, defined as having evidence of associated of one or more of either common blue, cellular blue, intramucosal, compound, and spindle cell, similar to the nomenclature for skin lesions, have also been rarely reported (7).

B. Pathology

The developmental features of oral melanocytic nevi are thought to mirror those developing in cutaneous locations. The melanocytic cells begin with growth in the epithelium at the junction of subepithelial-epithelial tissue and then develop in the subepithelial tissue as separate nests. These nevi are termed compound intraoral melanocytic nevi. Over time, the intraepithelial (junctional) component vanishes, with only the nevus cells present in the subepithelial tissue remaining, resulting in the common type, intramucosal melanocytic nevus.

The histologic features of oral nevi also mirror those of the skin. The nevus cells are usually round to oval in shape, although there may be some variation in some of the cells size. Junctional nevi reveal nevomelanocytes at the junction of the mucosal epithelium and submucosal connective tissue arranged in small nests. Compound nevi are composed of nevomelanocytes at the junction but also with nests of nevus cells in the subepithelial connective tissue. Intramucosal nevi, the counterparts to intradermal nevi in the skin with the entire nevomelanocytic proliferation confined to the subepithelial submucosal connective tissue, show nonencapsulated nevus cells in small clusters and aggregates (Fig 5). Common blue nevi show elongated dendritic-like processes associated with melanin pigmentation (Fig. 6). Cellular blue

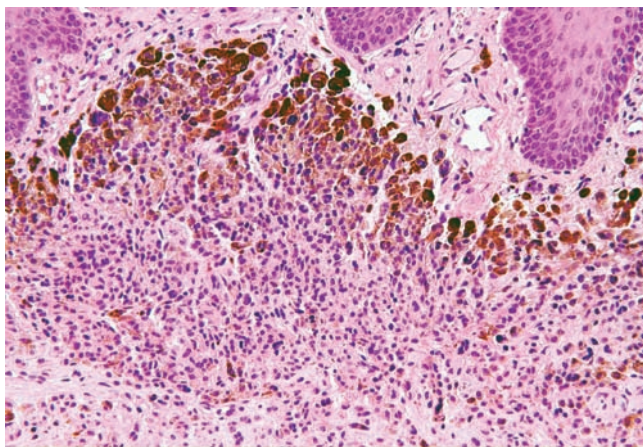


Figure 5 Oral intramucosal nevus. Clusters and theques of nevus cells with substantial melanin pigmentation is seen in this typical intramucosal nevus.

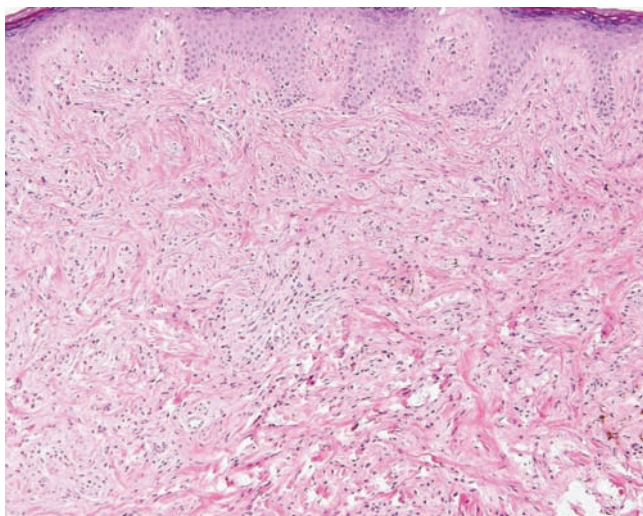


Figure 6 Oral common blue nevus. Spindling of the melanocytes and diffuse melanin pigmentation is noted in this oral mucosal blue nevus.

nevi are characterized by a clump of rounded to oval melanocytes containing melanin pigment.

C. Differential Diagnosis

Besides melanocytic lesions, focal pigmented lesions in the oral cavity include foreign bodies, ecchymosis, hemangiomas, and neoplasms. Systemic disorders and drugs also result in intraoral pigmentation. Drugs such as amiodarone, chlorpromazine, minocycline, and antimalarials may cause pigmentation, as can systemic conditions, including Peutz-Jeghers syndrome, Addison disease, and neurofibromatosis

(8–11). Foreign bodies may include diverse material such as graphite (pencil lead), ink, and medicaments, beside the most common, amalgam, used in dental procedures.

Oral melanotic macules should be considered in the differential diagnosis of oral nevi, as they are the most common pigmented melanocytic lesions in the oral cavity. These lesions may be blue, brown, or black. They are usually less than 1 cm in diameter and have a predilection for the lower lip and gingiva, as opposed to oral nevi. They are usually solitary and seen in patients over 40 (12). Histologically, they show melanin production in the basal cell layer, lamina propria, or both. They do not show increased melanocyte proliferation and they are not associated with elongated rete ridges.

Melanomas do occur in the oral cavity but are relatively rare (1). Common blue nevi are not considered by most authorities to be associated with development of melanoma, but whether other types of oral melanocytic nevi are precursors to melanoma is difficult to determine. As noted, the palate is the most common site of intraoral melanocytic nevi as well as the most common site for intraoral melanomas. Some reports of intraoral melanoma have described pre-existing clinical pigmentation of the mucosa in the affected area.

D. Treatment and Prognosis

Evaluation by epiluminescence microscopy (dermoscopy) has been advocated for evaluation of pigmented lesions of the oral cavity (13). Excision of suspected oral nevi is highly recommended since it may not be possible to clinically differentiate them from oral melanoma (8).

IV. AMALGAM TATTOO

Amalgam tattoos result from the unintentional insertion of amalgam restorative material into the soft tissues during dental procedures (1). Amalgam tattoos are commonly seen in the buccal, gingival, and alveolar mucosa, but the mandibular arch may be the most common site (2). The reported incidence of amalgam tattoo has been reported to be 1.0% to 1.3% in two patient-based series of biopsied oral lesions in oral pathology practices (2,3). Likely, the incidence is much higher, as lesions identified clinically as amalgam tattoo are usually not biopsied.

In a study of 20,731 surgical specimens described clinically as pigmented lesions from an oral biopsy service, 268 cases were of amalgam tattoos, 105 were of melanotic macules, and 32 were melanocytic nevi (3).

Amalgam contains mercury, silver, and tin. Mercury and tin may be absorbed into the blood stream, leaving primarily silver to corrode, although energy-dispersive studies reveal that all these elements are to be found in an amalgam tattoo. Numerous reports in older literature suggest that the elements in amalgam have been responsible for a wide variety of systemic symptoms. The presence of

these materials within the oral submucosa has never been reliably associated with any local or systemic symptoms (4).

A. Clinical Features

Clinically, amalgam tattoos may be solitary or multiple but are asymptomatic. Their coloration is gray or dark blue-black in appearance (Fig. 7). The blue-black coloration seen clinically is due to the electrolytic corrosion of the amalgam. Most amalgam tattoos measure less than 0.5 cm in greatest dimension (2). They appear generally as macules and may have either defined or irregular borders. The pigmentations observed are seldom palpable, although in some cases formation of submucosal fibrosis during the formation of the tattoo may remain palpable for years. Over time, amalgam tattoos may clinically enlarge. This may be due to spreading of amalgam particles by engulfing macrophages (5).

The clinical differential diagnosis includes other pigmented intraoral lesions, including melanocytic nevus, oral melanoma, and oral melanotic macule. Varicosities with and without thrombi formation may also be clinically similar to tattoos. Various chemicals and drugs may cause pigmentation, including cisplatin, arsenic, and bismuth. Occupational exposures to mercury and lead may also lead to oral pigment deposition.

Unintentional oral mucosal tattoos may also be found in patients with no history of amalgam placement. In these patients, the source of the accidental foreign material placement is often a graphite pencil point.



Figure 7 Amalgam tattoo. Commonly identified intraorally, amalgam tattoos are typically grey to black depending in part on the amount and type of foreign material introduced into the submucosa. Other sources of “accidental” oral tattoos include graphite from pencils. If enough foreign material is present, it can often be seen on a dental radiograph.

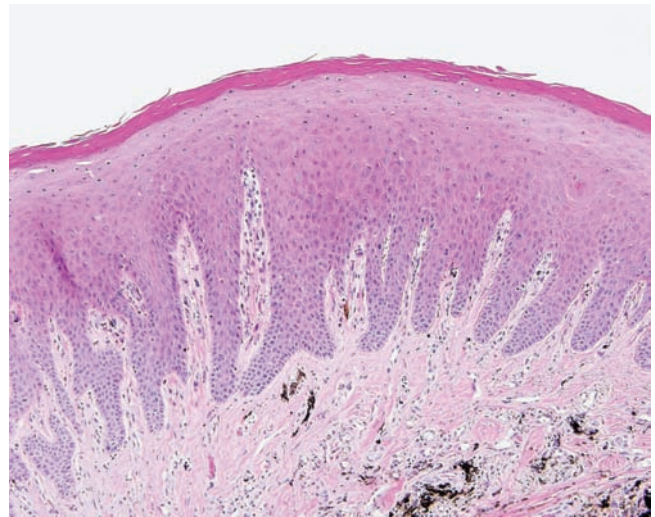


Figure 8 Amalgam tattoo. Black, foreign material is distributed throughout the submucosa. Some tattoos will show microscopic evidence of a reactive infiltrate of lymphocytes, plasma cells, and macrophages. Other tattoos show remarkably little inflammation.

B. Pathology

Microscopically the amalgam material is usually seen just in the superficial submucosa but may be seen deeper (Fig. 8). The black to dark brown material can be seen in macrophages and giant cells but also in fibroblasts, collagen, elastic fibers, blood vessel walls, and endothelial cells (3). The pigmentation can also occur in the minor salivary glands, nerves, skeletal muscle, and the basement membranes of the mucosa (1,3). In nearly half of all cases, there is no inflammatory reaction, but one study reported 17% of cases to have a macrophage response and 38% to show a chronic response with foreign body granuloma formation with multinucleated giant cells (3). Asteroid bodies may also be seen (3). Energy-dispersive microanalysis reveals silver, tin, mercury, and copper in the pigment (1,6,7).

C. Treatment and Prognosis

Amalgam tattoos do not need to be treated since they do not cause any local or systemic disease. The only reason for biopsy is if other lesions of concern such as melanomas cannot be excluded on the basis of the clinical appearance. Amalgam tattoos may also be excised if they involve the lips and are a cosmetic concern.

V. BENIGN MIGRATORY GLOSSITIS (GEOGRAPHIC TONGUE)

Benign migratory glossitis (geographic tongue) is usually an asymptomatic inflammatory disorder of the tongue mucosa. The condition has a large number of synonyms, including erythema migrans, superficial

migratory glossitis, pityriasis linguae, glossitis areata migrans, exfoliatio areata linguae, and lingual dystrophy. The term "migratory glossitis" is a good descriptor, as the lesions appear to change location or migrate, in pattern and size, sometimes within hours or days. The descriptor geographic (geographic tongue) is applied to the patterned lesions because of the similarity to the viewing of an aerial map of land masses (1,2).

The prevalence of the lesion varies by report but is generally thought to be between 1.0% and 2.5% of the population (3–8). It is more common in children in some series (9).

Some studies show a female predominance but others show the lesion affecting males equally.

The process is poorly understood but has been associated with nutritional deficiencies, anxiety, psoriasis, and lichen planus. Reiter syndrome has also been associated. However, a genetic predisposition is often present and the process often occurs with fissured tongue. Histocompatibility antigens DR5 and DRW6 have been seen to be increased in patients with geographic tongue (10). Interestingly, both psoriasis and benign migratory glossitis are associated with HLA-Cw6 (11,12). Further, the histologic appearances may mimic that of psoriasis. Conflicting views exist about the association with diabetes. Patients with atopy, including asthma, hay fever, or eczema are more likely to have geographic tongue (13). Hormonal associations also have been noted, including timing with oral contraceptive cycles.

A. Clinical Features

Benign migratory glossitis is most often asymptomatic, although some patients complain of irritation when eating spicy foods. If patients complain of symptoms such as burning, there can be a secondary condition such as oral candidosis. The lesions appear as multifocal, rounded, or irregular flat, red patches usually with an elevated white border composed of aggregated papillae (Fig. 9). Only a single lesion may be seen in some patients. Most commonly affected areas are on the dorsum of the tongue, followed by the lateral margins, or the tip of the tongue (14,15).

B. Pathology

Histologically, there may be an acute and chronic inflammatory infiltrate in the submucosa from the center of the lesion with epithelial edema and neutrophils. Epithelial regeneration is present. Neutrophilic microabscess formation, similar to Munro microabscesses, is typical. The epithelium of the hypertrophic margin of the lesions is parakeratotic (1). These features often bear a striking resemblance to epidermal psoriasis (Figs. 10,11).

C. Differential Diagnosis

Benign migratory glossitis is most often diagnosed entirely on the basis of its clinical features. If an



Figure 9 Benign migratory glossitis. Multiple foci of filiform papillae atrophy leaving smooth, red macules, bordered on some sides by thin hyperparakeratotic rims is clinically diagnostic for benign migratory glossitis (geographic tongue, erythema migrans).

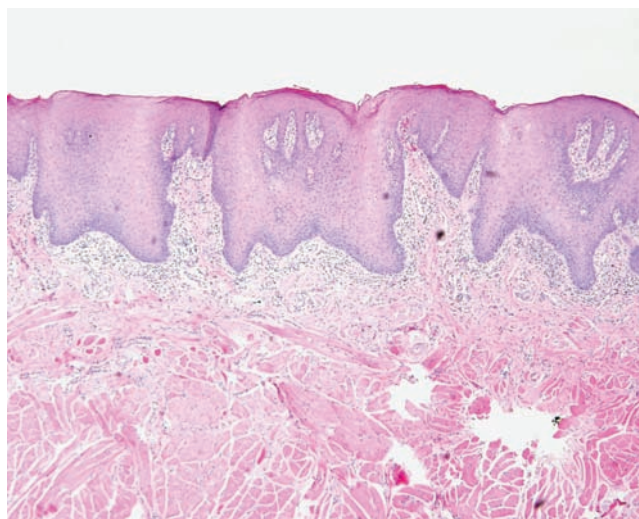


Figure 10 Benign migratory glossitis. The surface epithelium shows loss of the normal overlying filiform papillae, replaced by areas of irregular acanthosis or areas of atrophy. The epithelium shows no evidence of cellular atypia. A chronic infiltrate of lymphocytes, plasma cells and neutrophils is seen in the submucosa.

incisional biopsy is performed, the differential diagnosis would include other noninfectious inflammatory diseases such as lichen planus. However, neutrophils and microabscess formation should not be found in lichen planus. In symptomatic cases, evidence of a secondary candidosis can be found.

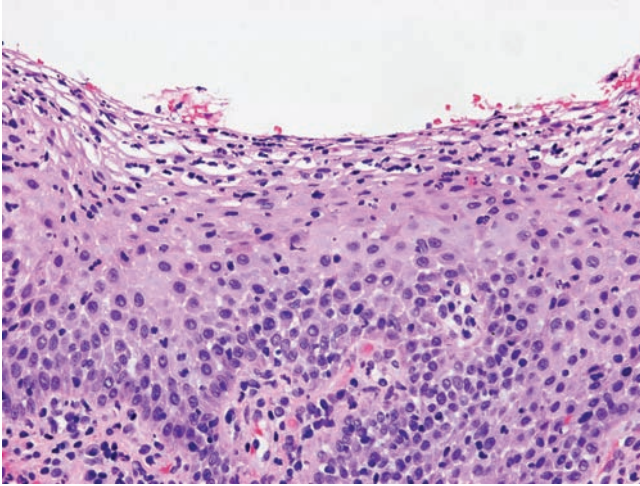


Figure 11 Benign migratory glossitis. Areas of alternating acanthosis and atrophy are seen in the stratified squamous epithelium. Psoriasisform pockets of neutrophils are often seen in the superficial stratum spinosum.

D. Treatment and Prognosis

The lesions require no specific treatment, but the patient may require explanation that the lesion is not malignant or premalignant (16). Some authorities believe that cases in which the patient can clearly identify a precipitating cause, removal of the stimulus may help, but this is not universally accepted.

VI. MEDIAN RHOMBOID GLOSSITIS

Median rhomboid glossitis is a depapillated round or rhomboid, smooth, pink or erythematous, nodular area found on the mid-dorsal surface of the tongue just anterior to the circumvallate papillae (Fig. 12).



Figure 12 Median rhomboid glossitis. A focus of papillary atrophy on the dorsal tongue midline, just anterior to the circumvallate papillae. The shape is often, but not always rhomboid.

Synonyms include central papillary atrophy, posterior midline atrophic candidiasis, and posterior lingual papillary atrophy. The prevalence in the general population is approximately 0.2%. It is more common in elderly patients and relatively rare in healthy children (1,2).

Median rhomboid glossitis has been considered under a wide variety of etiologies, including inflammatory processes, developmental origins, or local alterations in blood supply. The area affected is the posterior dorsal aspect of the tongue. Some have suggested that there is a defect in the fusion at the posterior aspect of the paired lingual (lateral) tubercles that form the tongue during embryogenesis, which results in a depapillated surface. Others indicate that this area is also prone to an impaired blood supply. The majority opinion, however, is that median rhomboid glossitis is a chronic atrophic epithelial reaction to *Candida*. (3,4) *Candida* organisms, however, are not found in all cases.

Experimental work in rats does indeed reveal that long-term *Candida* infection may result in histologic changes similar to those seen in median rhomboid glossitis (5). A few cases have been associated with *Actinomyces* (6). A decrease in Langerhan's cells has been noted, which suggests a localized defect in immune surveillance (7).

Smoking and denture wearing may also contribute to the abnormality by favoring an environment for *Candida* proliferation. (8) It is also not uncommon in patients with acquired immunodeficiency syndrome (9,10). Diabetes, highly associated with oral candidiasis, is also linked with median rhomboid glossitis. The lesion may be an indicator of severity or extent of disease, as diabetic patients with median rhomboid glossitis have been reported to be more likely to have a longer duration of insulin-dependent diabetes mellitus and complications of nephropathy and retinopathy (11,12). Median rhomboid glossitis has also been associated with amyloid production, presumably because of chronic inflammation (13).

A. Clinical Features

Median rhomboid glossitis presents as a red lesion in the midline of the tongue, anterior to the circumvallate papillae, and most lesions are less than 2 cm (14). There is depapillation that is oval, rhomboid, or diamond shaped. This area may be flat or slightly raised and nodular. Because it is red with surface changes, it can be occasionally confused clinically with erythroplakia. An adjacent palatal mucosal focus of inflammation often termed a "kissing lesion" has been noted in patients with median rhomboid glossitis (15).

B. Pathology

Histologically, median rhomboid glossitis shows filiform papillae atrophy, parakeratosis, and irregular acanthosis. Both the fungiform and filiform papillae are diminished or absent (Fig. 13). The rete can

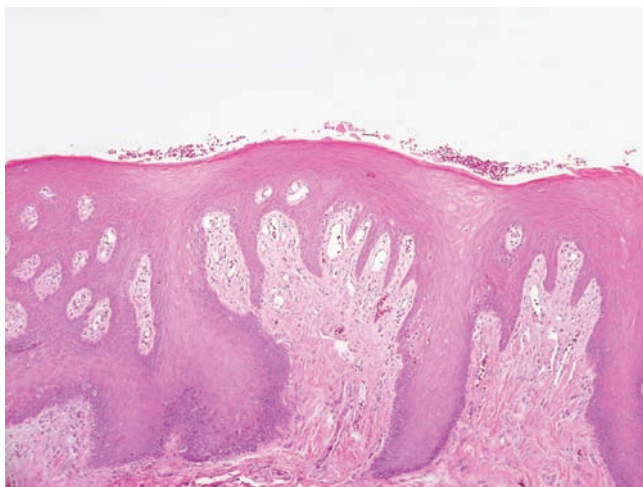


Figure 13 Median rhomboid glossitis. The overlying papillae architecture is replaced by irregular areas of epithelial acanthosis or atrophy. Candidal hyphae and spores are often noted in the superficial stratum spinosum. The underlying fibrovascular connective tissue will show a moderate to dense infiltrate of lymphocytes, plasma cells, macrophages, and neutrophils.

become elongated and lead to the forming of “test-tube” rete ridges. Pseudoepitheliomatous hyperplasia may be quite marked. Candida pseudohyphae and spores are seen in the upper layers of the epithelium in many cases. A chronic inflammatory cell infiltrate primarily made up of lymphocytes, plasma cells, and macrophages as well as some fibrosis and hyalinized changes may be seen in the submucosal tissues (1,16–19).

C. Differential Diagnosis

This site-specific lesion is most often diagnosed on the basis of its clinical presentation alone. In some rare instances, Kaposi’s sarcoma of the dorsal tongue in patients with acquired immunodeficiency syndrome may have resemblance to median rhomboid glossitis (10). The histologies differ, as the atypical vascular proliferation and spindle cell proliferation is not seen in median rhomboid glossitis. Since median rhomboid glossitis is a red mucosal area of the oral mucosa, erythroplakia might be considered clinically and result in a biopsy to rule out a pre-invasive squamous lesion. Rarely, invasive squamous carcinoma may mimic median rhomboid glossitis (20). Histologically, the pronounced pseudoepitheliomatous hyperplasia may be so marked that a diagnosis of well-differentiated squamous carcinoma may be entertained. Clinical information pertaining to the site and appearance of the tongue lesion would be useful in the evaluation of such lesions. However, the epithelial hyperplasia in median rhomboid glossitis does not show a desmoplastic response nor are there other architectural changes of invasion carcinoma.

D. Treatment and Prognosis

Therapy for median rhomboid glossitis is controversial. Some authors recommend treatment of patients with antimycotic agents, but others suggest that antifungal treatment is unwarranted and does little to affect the course of the condition unless the cause of the opportunistic infection is identified and eliminated. Cessation of smoking and correcting denture problems or limiting denture wearing may help in some patients in whom these issues are noted.

VII. NICOTINIC STOMATITIS

Nicotinic stomatitis (also known as smoker’s palate) presents clinically with the appearance of hyperkeratosis of the hard and/or soft palatal mucosa with multiple small red dots corresponding to the orifices of minor salivary gland ducts (1–6). Nicotinic stomatitis is seen almost exclusively in pipe smokers with intense usage, but cigar and cigarette smokers are not immune (7). Some believe that the response is primarily due to a response to heat rather than tobacco smoke by-products, although these two causes are difficult to separate. Some patients that do not smoke but consume very hot liquids may develop a similar process. Men are more frequently afflicted than women.

A. Clinical Features

Nicotinic stomatitis is asymptomatic. It characteristically occurs posterior to the palatal rugae. The small erythematous areas seen clinically represent dilated and inflamed openings of the minor salivary glands surrounded and made more clinically prominent by surrounding hyperkeratotic palatal mucosa (Fig. 14). Splitting or fissuring of the mucosa is seen in cases



Figure 14 Nicotinic stomatitis. There is widespread, relatively uniform hyperkeratosis of the posterior hard and anterior soft palatal mucosa in this chronic pipe smoker. Multiple small erythematous nodules representing inflamed minor salivary gland ducts are seen.

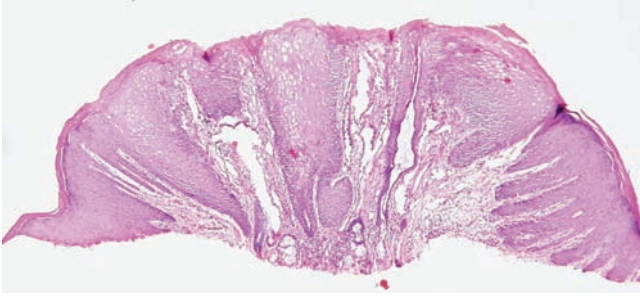


Figure 15 Nicotinic stomatitis. The overlying stratified squamous epithelium shows extensive hyperparakeratosis, hyperorthokeratosis, and mild acanthosis with no evidence of cellular atypia. The submucosa contains a mild to moderate infiltrate of lymphocytes, plasma cells, and neutrophils. Some sections can show inflamed minor salivary gland ducts, often with squamous metaplasia.

where the hyperkeratosis is prominent giving a nodular appearance in advanced stages. The mucosa can assume a grayish white or brown coloration because of extrinsic staining, similar to that seen in hairy tongue.

B. Pathology

Histologically, there is hyperortho- or parakeratosis and acanthosis of the palatal epithelium and lymphocytic inflammation of the subepithelial tissues (Fig. 15). There should be no evidence of epithelial dysplasia. Squamous metaplasia of the minor salivary gland ducts can be seen in some cases but is not necessary for the diagnosis (8,9).

C. Treatment and Prognosis

Nicotinic stomatitis is not a premalignant lesion, but tobacco exposure places the entire upper airway at risk for dysplasia and carcinoma. Therapy is cessation of smoking and the tissue may return to normal appearance in as little as one to two weeks.

VIII. HAIRY TONGUE

Hairy tongue is a benign condition characterized by hyperkeratosis and enlargement of the filiform papillae. Whether there is an overproduction of keratin or a loss of the ability to desquamate keratin is not known and both processes may be at work. The elongated filiform papillae also characteristically trap desquamated cells and bacteria (1,2). Synonyms include black hairy tongue, lingua villosa nigra, melanotrichia linguae, and hyperkeratosis of the tongue (3). The prevalence of hairy tongue varies. In a study in Jordan of over 1000 patients of all ages, 3.4% had hairy tongue (4). Most of these patients were males and were smokers. In contrast, in a study of over 3600 school children from Minnesota, only two had hairy tongue (5).

Usually the area affected is the dorsum of the tongue immediately anterior to the circumvallate papillae, but lateral and anterior distribution has been described (6,7). Often this hyperkeratosis is darkened and maybe known as black hairy tongue. Other colors include dark green, yellow, or brown.

It is thought that the coloration most often arises from tobacco or food products such as coffee or tea. Hairy tongue is more common in elderly patients and those with chronic illness with limited food intake. In these instances, it is attributed to the lack of friction food produces during mastication, but poor hygiene practices are likely contributory as well (8–12). Vitamin deficiency and use of mouth washes have also been implicated. The pH of the tongue surface has been noted to be below 6 in many patients (13). Hairy tongue is often reported in patients who have taken a wide variety of antibiotics and phenothiazines (14–16). It has also been linked to smoking, but the amount of tar and nicotine consumed daily does not necessarily correlate with its presence (17).

A. Clinical Features

Patients frequently are asymptomatic but may complain of bad breath. Hairy tongue presents as an irregular, often dark brown to black plaque that can be removed partially by vigorous scraping. The enlarged and the elongated papillae give the surface of the tongue a hair-like appearance, sometimes described as furry (Fig. 16). The medial aspect of the dorsal surface of the tongue is most often affected, but the process may be localized unilaterally (18).

In the clinical differential diagnosis, hairy tongue should be separated from oral hairy leukoplakia, with which it has significantly different histologic and clinical appearances as well as etiologic origins (19).



Figure 16 Hairy tongue. There is profound hyperkeratosis of the filiform papillae on the dorsal tongue. The increased keratosis is usually most prominent near the midline, just anterior to the circumvallate papillae. The keratin will retain a variety of extrinsic products and is further colored by numerous bacteria and fungal colonies.

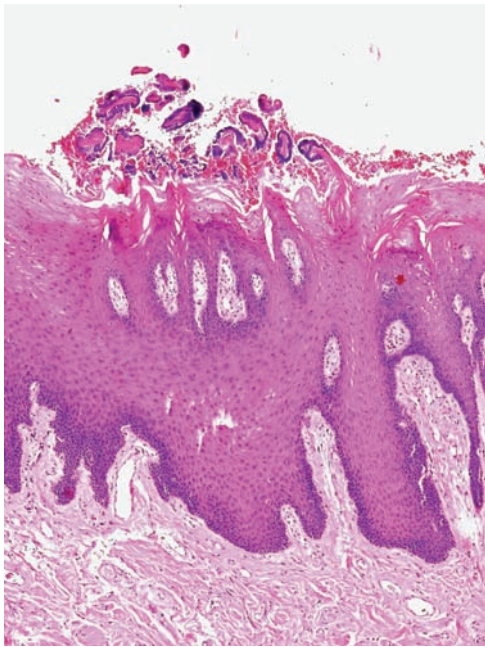


Figure 17 Hairy tongue. There is profound hyperparakeratosis of the filiform papillae. Numerous bacterial and fungal organisms are seen among the hyperkeratotic layers. The stratified squamous epithelium should show no evidence of cellular atypia.

B. Pathology

Hairy tongue is not always biopsied because the clinical appearance is characteristic. Histologically, the elongated papillae show marked surface hyperkeratosis and trapped microorganisms (Fig. 17). The lamina propria may show a mild lymphocytic infiltrate. Immunohistochemical studies have shown that there is retention of cells expressing the hair-type keratins (20). Electron micrographic studies have shown abnormally long secondary papillae with the surface squamous cells arranged in a fish scale or roof tile pattern. These orthokeratinized cells are often coated with microorganisms (21,22).

C. Treatment

A variety of treatments have been proposed with brushing or light scraping of the tongue, the most effective and most recommended (11). Treatment with isotretinoin has been attempted as well as podophyllin (23–26).

IX. ORAL HAIRY LEUKOPLAKIA

Oral hairy leukoplakia is observed mainly in individuals with HIV infection (1–8). Most HIV-positive patients do not have AIDS at the time of diagnosis of oral hairy leukoplakia, but AIDS develops later in a high percentage (1). Oral hairy leukoplakia is only second in frequency to oral Candidiasis in HIV-positive persons with frequencies ranging from 20% to nearly 50%, and patients with overt AIDS often have a higher incidence (9).

Oral hairy leukoplakia often does not occur alone. Other oral pathologies are evident, and *Candida* hyphae are reported to be present in as many as 50% of oral hairy leukoplakia lesions (6,10). It is most often identified in males with male-to-male HIV risk behaviors. It is rare in children (3,11). Reports appear mixed as to whether treatment of patients with AIDS using multidrug therapy (highly active antiretroviral therapy, HAART) has successfully decreased the incidence of oral hairy leukoplakia (7,12–14).

Oral hairy leukoplakia is caused by Epstein-Barr virus (EBV) infection, and experimental work suggests that a recombinant variant of the EBNA-2 gene may play a role in the pathogenesis (15). Evidence suggests that CD4-positive T cells are involved in primary host defense and that low CD4 counts are responsible for oral hairy leukoplakia in HIV-positive patients (16,17). Where the EBV initiates the lesion is incompletely resolved. EBV is a ubiquitous herpes virus, and infection results in persistence of the virus for life, and a reservoir is thought to be B lymphocytes. Tongue epithelial cells in nonimmunosuppressed patients are usually not able to support EBV replication (18). However, even normal-appearing tongue epithelial cells in patients with a history of immune suppression have impairment of the immune system allowing EBV replication (15,19). The mechanism of action of EBV in oral hairy leukoplakia is complex, and some data suggest an interaction of blood and epithelial reservoirs of EBV in the pathogenesis of oral hairy leukoplakia (20). The presence of EBV DNA in basal and parabasal epithelial cells of the tongue supports the theory that hairy leukoplakia represents a reactivation of latent lingual infection (21). It is thought that the EBV evades mucosal immune response in oral epithelial infection possibly because of a relative decrease in Langerhan's cells (22).

A. Clinical Features

Oral hairy leukoplakia usually is asymptomatic. It is seen as a white and poorly demarcated, usually corrugated or furrowed and "hairy" lesion, although some lesions may be relatively flat. Most frequently, it involves the tongue bilaterally but may be unilateral, and other intraoral sites such the buccal mucosa have also been reported (23). The lesion does not regress after topical or systemic antifungal therapy.

Oral hairy leukoplakia may be mimicked by other diseases (10). The clinical differential diagnosis includes papillomas and oral warts. Chronic abrasion of glossal mucosa by the adjacent teeth can produce a hyperkeratosis of the lateral filiform papillae similar to that seen in oral hairy leukoplakia. Plaque-forming oral candidosis, also a common finding in immunosuppressed patients, can form rough white lesions virtually identical to oral hairy leukoplakia. Syphilis has also been reported to give a similar appearance (24).

Importantly, patients who are HIV-negative but are otherwise immunosuppressed may have oral hairy leukoplakia. Uremic stomatitis and ulcerative colitis have also been reported to be associated with lesions that appear histologically similar to oral hairy leukoplakia (25,26). While oral hairy leukoplakia is

often an oral manifestation of sexually transmitted disease, this is not always the case. Oral hairy leukoplakia has been described as an early indicator of EBV-associated posttransplant proliferative disorder and has occurred in HIV-negative patients with acute lymphocytic leukemia, multiple myeloma, bone marrow transplants, and other neoplastic diseases treated with immunosuppressive oncologic therapies (8,27–32). “Pseudo-oral hairy leukoplakia” has also been described in rare patients that have oral lesions with both clinical and histologic features of oral hairy leukoplakia but are HIV-negative, have no immunosuppression, and whose lesions do not demonstrate EBV (10,33). Because of these mimics, numerous authors recommend that diagnostic criteria for oral hairy leukoplakia include clinical, histopathologic, and immunohistochemical or molecular analysis (10).

B. Pathology

Although there are a number of histologic features that have been associated with oral hairy leukoplakia, these features are not always specific (23). The epithelium is characterized by hyperparakeratosis of variable thickness, acanthosis, and minimal-to-absent submucosal inflammation (Fig. 18). The tongue frequently shows hair-like projections of keratin (34). Often a band of parakeratin, sometimes with corrugation, can be seen sharply demarcated from the spinous layer. In the upper part of the spinous layer the EBV-infected cells often have the appearance of koilocytes. The cells show cytoplasmic ballooning or ground-glass change and intranuclear inclusions (35). *Candida* hyphae and spores are seen in many cases. Cytologic preparations have also been described for detection of oral hairy leukoplakia and to show condensation and margination of nuclear chromatin forming a bead-like appearance as well as intranuclear inclusions (36,37).

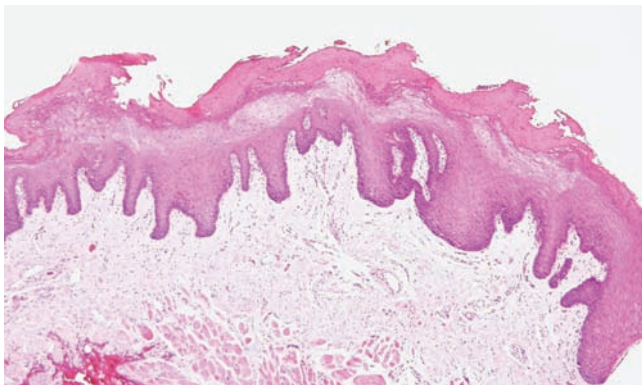


Figure 18 Oral hairy leukoplakia. The stratified squamous epithelium shows evidence of irregular hyperparakeratosis and acanthosis. The parakeratin often shows focal infiltration of fungal hyphae and spores. Koilocytes are found nested in the superficial stratum spinosum. The submucosa can show a chronic inflammatory cell infiltrate or be free of inflammatory cells presumably due to the patient's immunosuppressed state.

Many, but not all, authors believe that EBV should be demonstrated in tissue biopsies before a diagnosis of oral hairy leukoplakia is rendered. A variety of detection methodologies exist, including polymerase chain reaction (PCR) and in situ hybridization as well as immunohistochemistry (10,38–40).

C. Electron Microscopy

By electron microscopy herpes virus nucleocapsids can be demonstrated in the ballooned keratinocytes (35,41–44).

D. Treatment and Prognosis

Oral hairy leukoplakia is usually asymptomatic and often does not require therapy. If the lesions are symptomatic, then usually culprit is a secondary candidosis, and treatment with systemic or topical antifungals will be of value. Acyclovir and valacyclovir may be used for therapy, but some investigators have reported drug resistance, which may limit their usefulness.

X. FOCAL EPITHELIAL HYPERPLASIA (HECK'S DISEASE)

Focal epithelial hyperplasia is a benign hyperplastic lesion of the oral cavity that is caused by human papilloma virus (HPV) infection (1,2). It is commonly known as Heck's disease after publication of a study of primarily Native American Navajo children in 1965 (3). However, the literature indicates that the lesion had been described earlier in numerous reports (4–6).

Focal epithelial hyperplasia is much more common in certain ethnic groups such as Native Americans, Eskimos, and native people in Central and South America. It is relatively rare in Caucasians (4). In Native Americans, it is most commonly seen in children and teenagers. In Eskimos, the lesions have been found in all age groups with the highest prevalence in people older than 30 years. The lesions in Native Americans are most frequent in the mucosa of the upper lip followed by the buccal mucosa, commissures, and labial mucosa of the upper lip (7). In Eskimos, more than half the lesions are on the tongue (7). Focal epithelial hyperplasia has also been reported in an adult HIV-positive individual (8).

A. Clinical Features

The lesions present as circumscribed, sessile, soft, and elevated nodules of the oral mucosa (Fig. 19). Although beginning as separate nodules, the lesions often become confluent and cover large areas of the oral mucosa of the lips and buccal surfaces as well as the tongue.

B. Pathology

Histologically, the lesions show epithelial hyperplasia with acanthosis and elongation and anastomosing of



Figure 19 Focal epithelial hyperplasia (Heck). Multiple, sessile, smooth nodules involving any and all mucosal surfaces. The number and distribution of the nodules varies greatly from patient to patient.

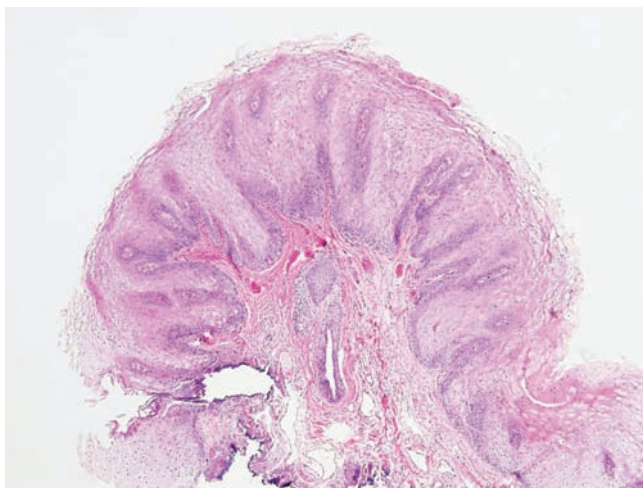


Figure 20 Focal epithelial hyperplasia (Heck). Focal areas of stratum spinosum show acanthosis and mild hyperparakeratosis. The lesions are well demarcated from the adjacent uninvolvement surface mucosa.

the rete ridges (Fig. 20). There is some resemblance to condyloma acuminatum. Koilocytes are often found. The lesions in focal epithelial hyperplasia do not form fibrovascular cores as seen in papillomas (1,2).

C. Molecular and Genetic Data

Multiple subtypes of HPV may be found in focal epithelial hyperplasia, but HPV types 13 and 32 are the most common (9). Other subtypes include HPV 6, HPV 16, and HPV 11.

D. Electron Microscopic Studies

Electron microscopic examination reveals viral particles (4).

E. Treatment and Prognosis

No treatment is generally required as the lesions frequently spontaneously resolve. The period of time for resolution is variable, usually months but some patients require up to a year or more for resolution. Focal epithelial hyperplasia is not considered premalignant (1,2).

XI. CONDYLOMA ACUMINATUM

A. Definitions and Synonyms

Condyloma acuminatum, also known as oral wart, venereal wart, verruca acuminatum, and moist wart, is caused by HPV and appears one to three months after exposure (1–3). Condyloma acuminatum most commonly involves anogenital sites. Lesions involving the oral mucosa were rarely reported until relatively recently (4,5). Condyloma acuminatum is most often associated with HPV subtypes 6 and 11 and is frequently seen in HIV-positive patients. Similar to anogenital condylomas, oral condylomas occur predominantly in young sexually active men in the third and fourth decades (6,7). Immunocompromised individuals, including those infected with HIV or organ transplant patients, are at an increased risk for oral condylomas. Some suggest that there is an increase in oral condylomas following use of HIV antiviral therapy, but this is controversial (6–10).

Oral condyloma is most commonly due to oral sexual contact. The occurrence of oral condylomas in young children and in patients with no sexual contacts provides support for transmission by other means, including autoinoculation, hematogenous spread, and maternal transmission (1).

B. Clinical Features

Oral condylomas may occur in conjunction with condylomas at other sites, but may occur in the absence of condylomas elsewhere. Most are asymptomatic but may be tender if secondarily inflamed. They may be multiple, and the most common sites are the upper and lower lips, lingual frenulum, and dorsum of the tongue. Other sites include the palate, buccal mucosa, and floor of the mouth.

Condylomas appear as soft verrucous nodules or multiple adjacent papillary clusters that tend to coalesce into soft, pink cauliflower-like masses, although isolated lesions may occur (11) (Fig. 21). They may also appear clinically as a diffuse verrucoid hyperplasia, an irregular exophytic mass with a granular surface or multiple sessile fibroma-like lesions (12). Clinically, condyloma may mimic other localized epithelial proliferative conditions, including Heck's disease, verruca vulgaris, squamous papilloma, or verrucous carcinoma (7).



Figure 21 Condyloma acuminatum. Rough, exophytic, sessile, papillary projections, occurring singularly or in groups. They may involve any oral mucosal surface but are most often noted to involve soft palatal or floor-of-mouth mucosa.

C. Pathology

Usually condyloma acuminatum has a pronounced spinous layer hyperplasia and cellular ballooning, and mitoses are seen extending into the spinous layer (Figs. 22,23). The base of the rete ridges are often bulbous. The lesions show parakeratosis, acanthosis, and papillomatosis. Frequently a mild lymphoplasmacytic infiltrate is seen. Usually the base is sessile, and there is parakeratin crypt formation (1,7). These parakeratin crypts invaginate into the spinous layers. Condylomas often show koilocytes or paranuclear clearing, but frequency of these findings is variable in the literature (1,7,11). The squamous proliferation seen in Condyloma acuminatum has also been reported to involve excretory ducts of minor salivary glands.

Malignant transformation of oral cavity condyloma appears to be rare as opposed to condyloma

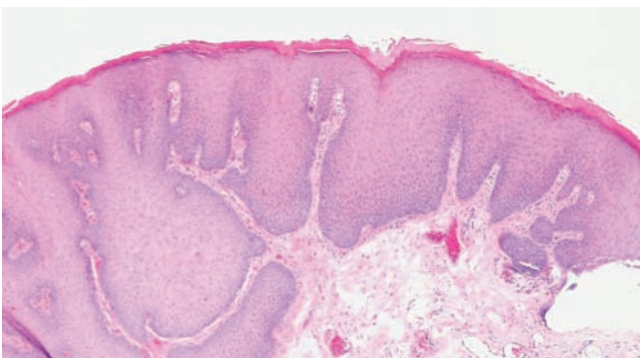


Figure 22 Condyloma acuminatum. Marked stratum spinosum acanthosis is present.

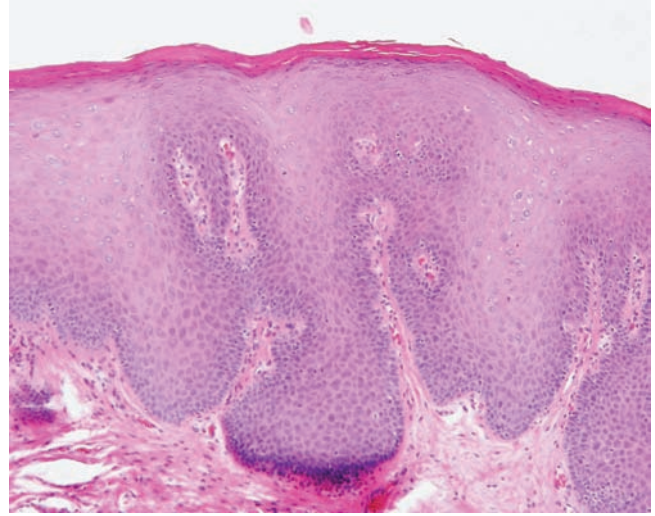


Figure 23 Condyloma acuminatum. The epithelium shows evidence of profound stratum spinosum acanthosis-forming broad, bulging rete ridges. There is often mild hyperparakeratosis. Koilocytes can often be noted but are not numerous. There should be no evidence of dysplasia.

acuminatum occurring in the anogenital regions. However, dysplastic change may be detected, particularly in those occurring in the presence of HIV infection (13).

D. Differential Diagnosis

The microscopic differential diagnosis includes verruca vulgaris, papilloma, and verrucous carcinoma (12). Verrucae are typically sessile, circumscribed, exophytic growths with elongated rete ridges often forming a radial pattern pointing toward the center of the lesions. Additionally, verruca vulgaris has epithelial projections with more pointed ends (11). They exhibit hyperparakeratosis at the tips and sometimes show hyperorthokeratosis on the sides (11). Condylomas have a papillomatous surface, and the stratum corneum is usually only slightly thickened.

Histologically, condyloma can be difficult to separate from squamous papillomas at times, and koilocytes are not always present. Squamous papillomas are usually pedunculated and exophytic and tend to exhibit epithelial tissue projecting outward from a central vascular core of fibrovascular tissue (1).

E. Electron Microscopy

Electron microscopy reveals intranuclear viral particles, and the particles are most numerous in the superficial layers of the parakeratinized epithelium (3).

F. Molecular Genetic Data

HPV DNA may be found by immunohistochemistry or molecular techniques such as in situ hybridization.

These techniques usually reveal that the oral condylomas are caused by HPV types 6 and 11, but other types are sometimes found (14,15).

G. Treatment and Prognosis

The recommended therapy for single, localized lesions is excision. For widespread lesions, often noted in immunocompromised patients, biopsy for diagnostic purposes followed by ablation is recommended. Ablation can include, laser and topical applications of podophyllin, 5 fluorouracil (5-FU) or trichloroacetic acid (14). Intralesional antivirals have also been used (6). As expected, oral lesions may recur after treatment.

XII. VERRUCA VULGARIS

Verruca vulgaris is a warty exophytic lesion that resembles verrucae in other sites, including the skin. It is caused by the HPV (1,2).

A. Clinical Features

Young adults and children are most often affected. It is thought that autoinoculation of virus, possible from the hands, may be a factor in their intraoral development. Usually verruca vulgaris is solitary but may be multiple. Common sites include the lips, palate, alveolar ridge, and gingiva (3,4). Their appearance is similar to verrucae elsewhere with a wart-like surface that can have irregular white spires protruding from the surface of the mucosa (Fig. 24). Alternatively, they can be nodular plaque-like lesions. Verruca have an entirely exophytic growth pattern, a feature which can be of value in clinically distinguishing it from early verrucous carcinoma and papillary squamous cell carcinoma.



Figure 24 Verruca vulgaris. A rough, multi-spiked, exophytic, well-demarcated lesion that can involve any mucosal surface but is most often noted on labial or glossal sites.

B. Pathology

Histologically, verruca vulgaris in most cases reveals long vascular cores coated in thick layers of epithelial cells that form pointed projections (Fig. 25). Koilocytes are seen in the majority of lesions, and an inflammatory infiltrate may be present in the connective tissue cores. A granular layer is seen. There are variations in the histologic appearance of verruca vulgaris giving rise to a number of low-power patterns. These have been categorized as acropapilliform, acroform, and cryptoform (5). The acropapilliform has an abrupt cupped margin with papillomatous projections having both angulated and rounded, bulbous patterns. The acroform has abrupt margins showing acutely angulated verrucous projections. The cryptoform pattern has discrete margins but with minimal exophytic projections.

C. Molecular and Genetic Data

Many HPV types are seen in oral verruca vulgaris. HPV type 2 is relatively common, but types 1, 4, 7, and 57 have also been reported (2,6,7).

D. Differential Diagnosis

The histologic differential diagnosis includes benign and malignant lesions, including squamous papilloma, condyloma acuminatum, verruciform xanthoma, proliferative verrucous leukoplakia, verrucous carcinoma, and papillary squamous carcinoma (8–10).

Squamous papillomas may be difficult to distinguish from some verruca, but the former usually do not show a broad or as sessile base as seen in the latter. Papillomas also do not demonstrate a centerward curve of the outermost squamous proliferation

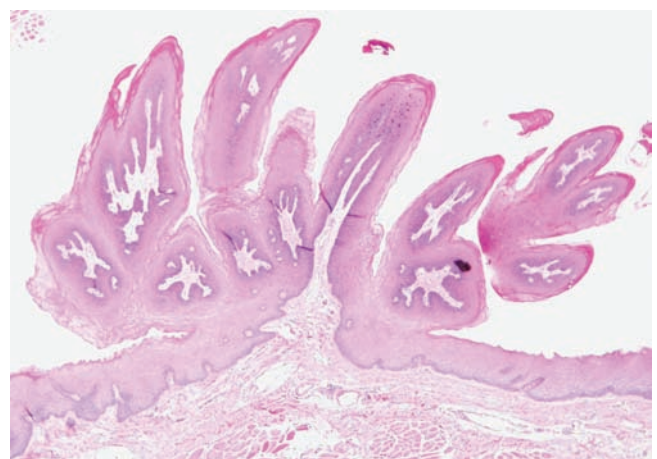


Figure 25 Verruca vulgaris. An exophytic, epithelial architecture with acanthosis, and hyperparakeratosis. The base can be sessile or pedunculated. Rete ridges often seem to radiate outward from a central point. The epithelial proliferation does not invade into the submucosa. Koilocytes are often noted. There should be no evidence of dysplasia.

papillae. Further, papillomas do not show a distinct granular layer or as distinct koilocytes as verrucae. Condyloma acuminatum does not have prominent verrucous projections and lacks a prominent granular layer. Verrucous carcinomas may resemble verruca vulgaris, but verrucous carcinoma extends deeply into the underlying stroma and most are larger than verruca vulgaris. Verruciform xanthoma has foamy cells just beneath the epithelial layer. Proliferative verrucous leukoplakia is not as localized as verruca vulgaris.

E. Treatment and Prognosis

Surgical excision is the treatment of choice, although some lesions may spontaneously regress. Recurrences, although unusual, are possible.

XIII. PAPILLOMA

Papillomas are among the most common of benign epithelial tumors of the oral cavity in both children and adults but are most commonly seen in persons of 30 to 50 years (1–3). Papillomas accounted for 1.5% of oral pathologies in a study of 2057 patient reports in a study from Singapore (4). Studies appear to be split as to whether females or males are more commonly affected (4,5). Most papillomas are less than 1 cm, and fewer than 10% are over 2 cm in size.

Most investigators regard papillomas as neoplastic, but some suggest that they are nonneoplastic, possibly a tissue reaction to injury (6). A high percentage of squamous papillomas are shown to have HPV sequences, and it seems likely that many papillomas are caused by HPV. While not all studies of papillomas reveal HPV sequences, it is likely that this may be due to the technique used for detection (1,7–11). Using the PCR, HPV can be found in a high percentage of oral scrapings or swabs from adults and children with no oral lesions (12–14).

A. Clinical Features

Papillomas are exophytic proliferations arranged in a finger-like configuration, giving a cauliflower-like clinical appearance (Fig. 26). Papillomas are usually solitary and reach their maximum size within a few weeks (2). Most are less than 1 cm in size. While the majority are pedunculated, some are sessile (7). Usually papillomas are white due to keratinization of the surface, but those without abundant keratin production may be pink. The tongue and palate are common sites of involvement (3).

B. Pathology

Squamous papillomas are small exophytic lesions with a central fibrovascular core covered by stratified, parakeratinized epithelium (3) (Fig. 27). A chronic inflammatory cell infiltrate can often be found in the otherwise bland fibrovascular connective tissue. Viral changes may be seen in the uppermost layers of the epithelial



Figure 26 Papilloma. A rough, often pedunculated, exophytic, well-demarcated lesion that can involve any oral mucosal surface.

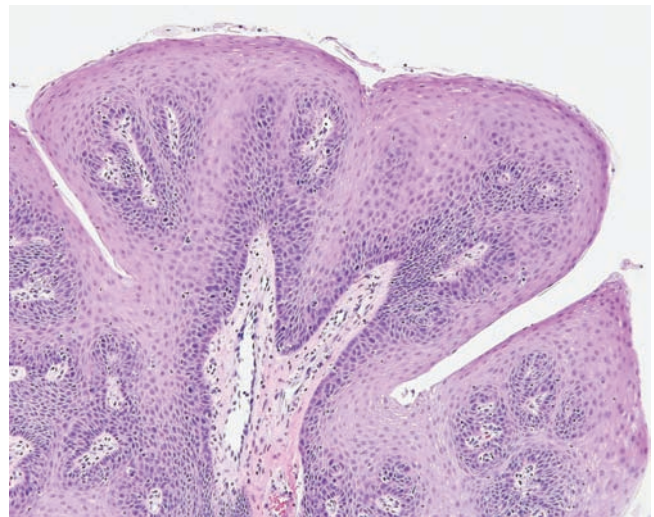


Figure 27 Papilloma. An exophytic, often pedunculated, tree-like proliferation of stratified squamous epithelium. Each epithelial branch has a core of fibrovascular connective tissue. There is no extension into the underlying connective tissue. There can be varying amounts of parakeratosis but without evidence of dysplasia.

cells. Papillomas can rarely show dysplastic changes, but this is uncommon in solitary papillomas (5).

C. Differential Diagnosis

Papillomas occurring singly must be differentiated from other conditions resulting in multiple papillomas of the oral mucosa, including Heck's disease, denture-related inflammatory papillary hyperplasia, and hairy tongue (2). Other papillomatous lesions include verruca vulgaris and condyloma (15).

Verruca vulgaris frequently mimics verrucae of the epidermis with a more sessile base than squamous papilloma and also show a more marked hyperkeratosis. Condylomas differ from papillomas in that condylomas are usually multiple, confluent, and larger than squamous papillomas. Condylomas histologically are also more likely to show parakeratin crypt formation and often show many more koilocytes (7,15).

D. Treatment and Prognosis

Treatment is conservative, complete surgical excision. Recurrence is unusual.

XIV. VERRUCIFORM XANTHOMA

Verruciform xanthoma was first reported in 1971 and is a rare lesion of the oral cavity that usually involves the buccal mucosa, gingiva, alveolar ridge, and, more rarely, the lip (1–3). The reported age range has been from 2 to 89 with a roughly equal female to male occurrence. Most lesions are less than 2 cm in diameter.

The cause is unknown but some authors favor an inflammatory origin. The inflammation has been proposed to be an aberrant response leading to foam cell accumulation, a viral or bacterial infection as an initiator of the inflammatory response, or a genetic predisposition leading to the accumulation of intracellular lipids. The foam cells represent histiocytes (4,5).

Some cases of verruciform xanthoma have been associated with other oral lesions or systemic conditions, including pemphigus, lipid storage disease, carcinoma in situ, warty dyskeratosis, graft versus host disease, lichen planus, discoid lupus erythematosus, and tobacco use (6–9).

Rare cases have been positive for HPV6/11 by in situ hybridization, but other authors have not been able to demonstrate HPV in these lesions (5,10,11).

A. Clinical Features

Clinically, verruciform xanthoma is well circumscribed and may be flat, papillary, or sessile. Many have a cauliflower-like roughened surface (12,13) (Fig. 28). They generally are slow growing. The lesions may be pink, red, yellow, or white, depending on the degree of keratinization (14). The margins are often sharply demarcated. The center of the lesion has been described as depressed, cup-shaped, or crateriform and may be ulcerated. Most lesions are asymptomatic and are detected incidentally.

Clinically, the differential diagnosis includes papillomas, verruca vulgaris, leukoplakia, carcinoma in situ, and verrucous carcinoma (6). Of these, most cases are clinically misdiagnosed as papillomas.

B. Pathology

Histologically, the lesions have a verrucoid surface with surface parakeratosis (2) (Fig. 29). The surface of the lesions can include a variety of different architectural appearances, including verrucous, papillary, or



Figure 28 Verruciform xanthoma. A well-demarcated, rough, hyperkeratotic, slightly exophytic soft tissue that can be found to involve any area of oral mucosa.

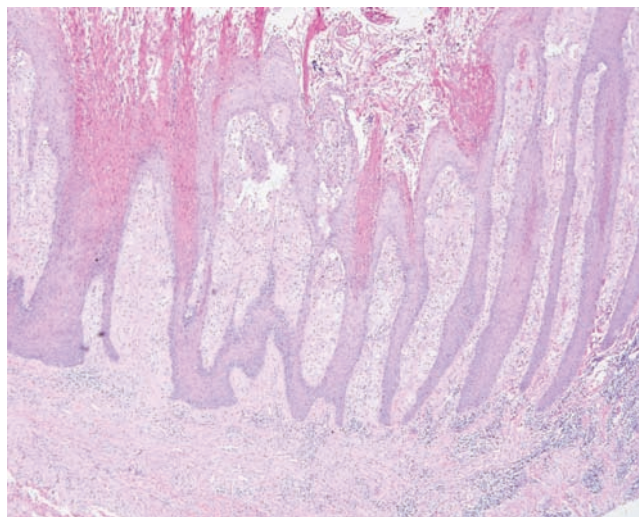


Figure 29 Verruciform xanthoma. At low microscopic power, a verrucous surface is evident.

minimally raised to flat. The verrucous pattern reveals a warty surface with marked hyperparakeratosis. The papillary pattern shows a less church-spire architecture than the verrucous patterns, and overall it is more exophytic. In the flat pattern the rete proliferates below the surface of the overlying epithelium. The rete shows relatively uniform hyperplasia. As the rete dips into the submucosa, the intervening spaces are filled with parakeratinized squamous plugs. In addition, the parakeratinized surface layer has a distinctive keratinization, which is more brightly eosinophilic on routine hematoxylin and eosin stained sections.

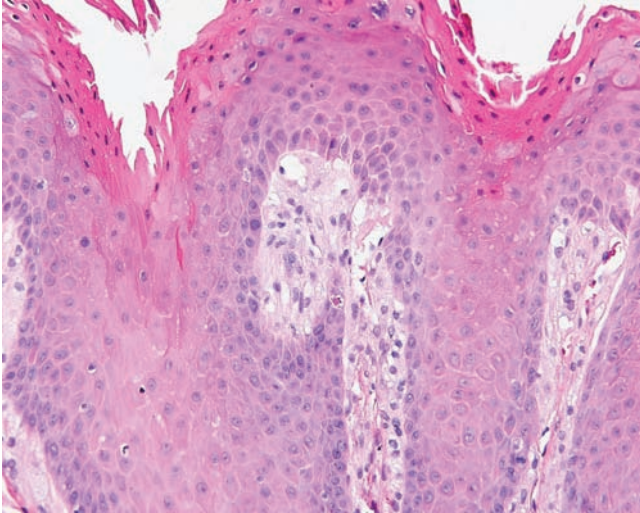


Figure 30 Verruciform xanthoma. The epithelium shows hyperparakeratosis with the formation of keratin plugs between acanthotic rete ridges. The papillary submucosa contains foamy histiocytes in varying numbers. There should be no cellular dysplasia.

In all the subtypes, there are varying numbers of xanthoma cells, which abut the basal layer of the squamous epithelium (Fig. 30). These xanthoma cells can be plentiful, occupying much of the papillary submucosa, or few in number and difficult to notice at low power. The cytoplasm of the foam cells may contain PAS-positive, diastase-resistant granules. Some cases have described occasional xanthoma cells infiltrating into the overlying epithelium (15).

C. Immunohistochemistry

The xanthoma cells stain with CD68 and other markers of histiocytic lineage but are frequently negative for S-100 (4,10,16–18).

D. Electron Microscopy

Ultrastructurally the xanthoma cells contain lipid and have characteristics of macrophages (13).

E. Treatment and Prognosis

The lesions are treated with conservative excision and are not considered premalignant. Recurrence is rare (14).

XV. DRUG-INDUCED GINGIVAL HYPERPLASIA

Drug-induced gingival hyperplasia may be caused by a variety of drugs, but several categories are particularly common and deserve mention, including phenytoin, cyclosporine, and calcium channel blockers, such as nifedipine (1,2).

A. Phenytoin

Phenytoin is an anticonvulsant drug used in a wide range of therapeutic modalities but particularly in seizure control. Gingival hyperplasia affects up to 50% of patients taking phenytoin, although some authors report much higher and lower percentages (3). Phenytoin-induced hyperplasia is usually evident within the first three months of starting the drug and is most rapid in the first year of administration (1). Studies have shown that phenytoin-associated gingival hyperplasia is exacerbated by chronic inflammation, including those caused by accumulations of bacterial plaque. Patients of a young age and those with higher serum phenytoin levels are also more likely to develop gingival hyperplasia (4).

Keratinocyte growth factor (KGF) levels have been noted to be elevated in drug-induced gingival hyperplasias (5). Both transforming growth factor (TGF)- β -1 and platelet-derived growth factor-BB levels have been shown to be increased in the tissues of gingival hyperplasia in patients receiving phenytoin (3). Extracellular matrix-degrading ability may be impaired by phenytoin as well as cyclosporine (6). There is also evidence that mast cell-mediated androgen action in the gingiva in response to phenytoin could cause gingival hyperplasia.

While phenytoin is the most common cause of drug-induced gingival hyperplasia, other anticonvulsants, such as phenobarbital, sodium valproate, and primidone have also been implicated (7). Other drugs reported to cause gingival hyperplasia include sertraline, vigabatrin, topiramate, lithium ethosuximide, ketoconazole, lamotrigine, cotrimoxazole, erythromycin, and oral contraceptives (2). Phenytoin-induced hyperplasias is halted but is not reversed by cessation of the medication.

B. Cyclosporine

Cyclosporine is a common drug for treating patients with renal transplant, and it is estimated that 20% to 35% of renal transplant patients have gingival hyperplasia as a result (8). Whether or not gingival hyperplasia secondary to cyclosporine A use is dose dependent is not clear (9). Concomitant use of ketoconazole, amphotericin B, and cimetidine increase the activity of cyclosporine A by decreasing its hepatic metabolism (9). Cyclosporine A has been shown to increase the production of collagen by fibroblasts. Cyclosporine increases the levels of interleukin-6, TGF- β -1, and FGF-2 and decreases gamma interferon, all of which are thought to increase collagen production (10). There is also a concomitant reduction in collagenase activity.

KGF is upregulated by cyclosporine, and studies have shown that the KGF receptor and the receptor mRNA are higher in epithelial cells in gingival hyperplasia compared with normal controls (5).

C. Calcium Channel Blocking Agents

Approximately 20% of patients taking nifedipine experience gingival hyperplasia. Other calcium

channel blockers such as verapamil, nitrendipine, felodipine, diltiazem, and amlodipine also cause gingival hyperplasia (11). Similar to cyclosporine and phenytoin, KGF levels are increased (5). Experimentally, nifedipine has been shown to increase p53-positive gingival epithelial cells (12). Conversely, others have found nifedipine to induce gingival hyperplasia in rats by inhibiting apoptosis rather than by stimulating keratinocyte production (13). Nifedipine may inhibit adherence and lipopolysaccharide-stimulated macrophage-induced death of fibroblasts (2).

D. Clinical Features

The gingiva in drug-induced hyperplasia is nodular and centered on the interdental papillae (14). While the gingival proliferation usually begins in the interdental papilla, it gradually moves to involve the gingival margins (Fig. 31).

E. Pathology

The histopathologic findings of these gingival hyperplasias are similar, regardless of the drug responsible (15). The epithelium shows irregular acanthosis with downward sharp rete ridge growth, sometimes in an interlacing reticular pattern (Fig. 32). The stroma shows spindling of fibroblasts and collagen deposition. These spindle cells may be arranged in a fascicular pattern. Scattered calcifications may be seen. A lymphoplasmacytic inflammatory infiltrate is often present.

F. Treatment and Prognosis

For phenytoin, treatment consists of stopping the drug if possible, but if regression does not occur, surgical remodeling of the gingiva may be necessary.

Cyclosporine A-induced gingival hyperplasia has been treated with azithromycin, as well as



Figure 31 Drug-induced gingival hyperplasia. Multinodular, firm proliferations of gingiva surrounding the teeth. Areas of inflammation, secondary to dental plaque and calculus accumulation will accelerate the formation and size of the proliferations.

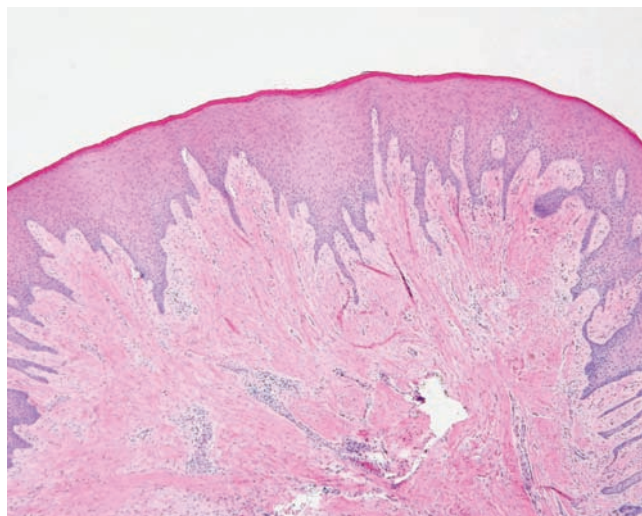


Figure 32 Drug-induced gingival hyperplasia. Reactive acanthosis with elongated rete ridge formation is noted in the otherwise normal overlying stratified squamous epithelium. The bulk of the clinically evident nodules are the result of hyperplasia of the underlying fibroblasts and accumulation of dense collagenous connective tissue. Chronic inflammation is often noted in the superficial submucosa.

metronidazole and other drugs derived from erythromycin (8). Optimum therapy is discontinuation of cyclosporine, but that is often not possible.

Surgical therapy, including gingivectomy and periodontal flap techniques have been used for treatment of gingival hyperplasia in patients receiving calcium channel blockers as well as cyclosporine A. These procedures reduce the tissue size for variable time periods but usually do not attain permanent results as long as the patient continues the drug. Discontinuation of calcium channel blockers in a series of peritoneal dialysis patients resulted in disappearance of the gingival hyperplasia within one month (11).

For all drug-induced hyperplasias, maintenance of optimal oral hygiene, which reduces gingival inflammation, is the best way to slow progression or recurrence of the hyperplastic tissue.

XVI. DENTURE-INDUCED FIBROUS HYPERPLASIA

Denture-induced fibrous hyperplasia is known by a variety of names, depending on the location or the cause. Synonyms include epulis fissuratum, denture injury tumor, denture epulis, denture hyperplasia, and denture-induced inflammatory hyperplasia.

Epulis is a general clinical term for lesions of the oral mucosa having a direct contact with the periodontal membrane or periosteum of the jaw. Denture-induced fibrous hyperplasia (epulis fissuratum) is a term usually reserved for hyperplastic, reactive tissues occurring along the flanges of upper or lower



Figure 33 Denture-induced fibrous hyperplasia (epulis fissuratum). Ridges and folds of linear soft tissue are characteristically adjacent to the acrylic flange of a full or partial removable denture appliance. The depth of the vestibule is often ulcerated due to chronic trauma from the denture flange.

dentures (1) (Fig. 33). The term “fissuratum” derives from the fissuring of the hyperplastic epithelium. The fissures can form multiple folds or flaps, with some folds overlying the ones adjacent, similar to pages in a book (1). In a study of 23, 616 Caucasian-Americans older than 35 years, denture-induced fibrous hyperplasia was seen at a prevalence of 0.4% (2). Generally, denture-induced fibrous hyperplasia is the result of chronic injury caused by ill-fitting dentures with repeated cycles of injury and repair building up a hyperplastic tissue response (3).

A. Clinical Findings

The clinical findings vary according to the degree and length of trauma, inflammation, and subsequent fibrosis caused by the denture. The lesion may be sessile or pedunculated and appears red and ulcerated or dense and fibrous (3). Those that are ulcerated can have some similarities to pyogenic granuloma. Lesions may be present for a few months to many years. Most cases occur in persons between 40 and 60 years, an age associated with denture use. Denture-induced fibrous hyperplasia is more commonly seen in women. The anterior portions of both jaws appear affected more than posterior locations, and more lesions are found on the buccal aspect than the lingual aspect (3). Occasionally, inflammatory papillary hyperplasia may coexist.

B. Pathology

The histologic differential diagnosis is usually not difficult, given the appropriate clinical history and findings (3). Histologically, the tissue shows dense, fibrous tissue hyperplasia with varying amounts of mixed chronic inflammatory cells (Figs. 34,35). The

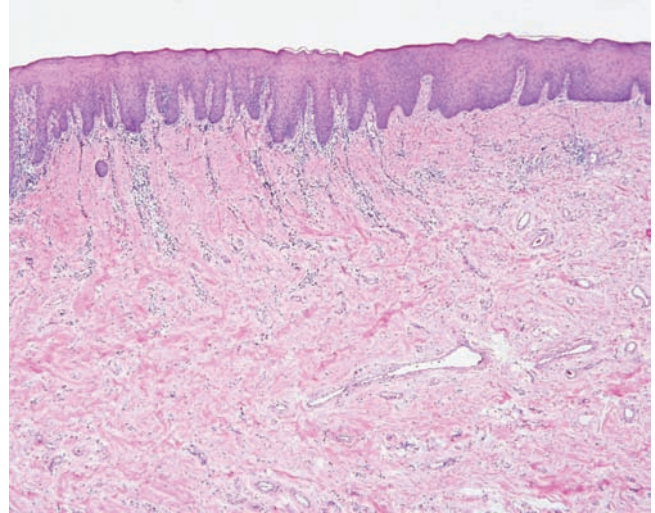


Figure 34 Denture-induced fibrous hyperplasia (epulis fissuratum). Marked acanthosis is present.

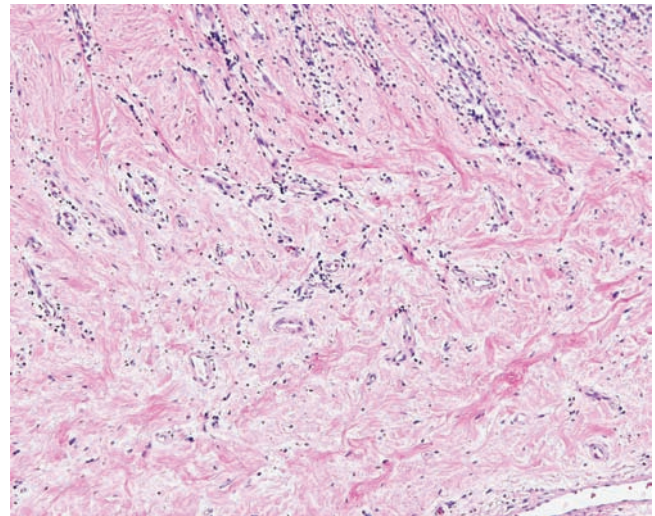


Figure 35 Denture-induced fibrous hyperplasia (epulis fissuratum). A chronic inflammatory cell infiltrate is noted in the superficial submucosa. The bulk of the enlargement is due to a reactive buildup of dense, fibrocollagenous connective tissue.

epithelial changes may show acanthosis and hyperparakeratosis focally. Many have pseudoepitheliomatous hyperplastic changes. It is thought that the pseudoepitheliomatous response is a more severe response to chronic trauma. In some cases, the epithelium splits in the center of the rete pegs, and this splitting or clefting can extend into the underlying connective tissue (3). The stromal component may resemble that of a dermal hypertrophic scar (4). Osseous and chondromatous metaplasia may be seen and should not be mistaken for sarcomatous changes.

C. Treatment and Prognosis

Treatment usually involves surgical removal. Denture adjustments or fabrication of new dentures may be necessary to prevent recurrence (4).

XVII. INFLAMMATORY PAPILLARY HYPERPLASIA

Inflammatory papillary hyperplasia is a reactive process that most often is caused by ill-fitting dentures or by dentures that are worn 24 hours daily. It is also known as denture stomatitis and denture papillomatosis, although this term can be reserved for denture-related inflammatory lesions that show no evidence of hyperplasia (1–3). Its prevalence may be 20% of all denture wearers. Thus, in some respects, its cause is similar to fibrous hyperplasia (*epulis fissuratum*), but its appearance and location differs. While denture-induced fibrous hyperplasia shows large ridges of redundant tissue predominantly at the margins of the denture, inflammatory papillary hyperplasia is marked by multiple small, wart-like or papillomatous projections most often under an upper denture involving palatal mucosa. It is most prevalent in patients who keep their dentures retained while sleeping or have poor oral hygiene. Candida has also been implicated in the etiology of inflammatory papillary hyperplasia, but its true role is not completely known (4). Inflammatory papillary hyperplasia may occur in patients without dentures. These patients often have a high palatal vault and are often predisposed to the development of oral candidosis by chronic xerostomia or use of steroidal inhalers. The process has also been reported in patients who are preferential mouth-breathers (5).

A. Clinical Features

Most cases are associated with a complete denture but partial dentures may also be at fault. While the palate is the most common anatomic site of involvement, inflammatory papillary hyperplasia may be seen under any part of any denture. The clinical findings are multiple small papillary growths separated by clefts (Fig. 36). The surface is often red, but pain is not a common complaint, and, in fact, most patients with inflammatory papillary hyperplasia are asymptomatic.

B. Pathology

The histologic appearance of inflammatory papillary hyperplasia are multiple, superficial squamous covered papillary projections (6). In many lesions, the appearances are those of pseudoepitheliomatous hyperplasia (Fig. 37). No epithelial atypia is present. The submucosal stromal tissue reveals a mixed, chronic inflammatory cell infiltrate. Involvement of submucosal salivary glands may result in a ductal squamous metaplasia, duct obstruction, and other features seen in sialadenitis or sialometaplasia.

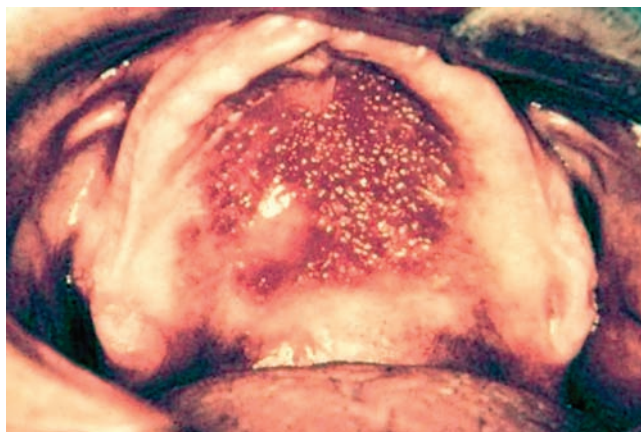


Figure 36 Inflammatory papillary hyperplasia. Multiple, erythematous papillary projections of soft tissue involving hard palatal mucosa. This is most often noted under a maxillary removable partial or full denture appliance, although the condition can also be seen as a result of nonspecific, chronic inflammation in patients with high palatal vaults.

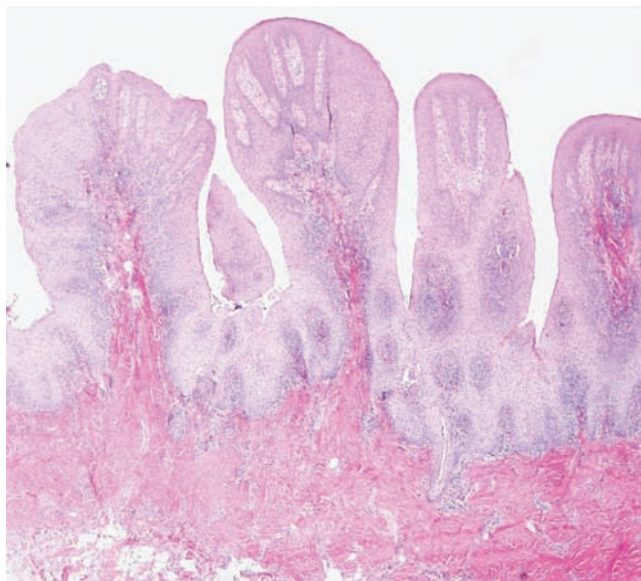


Figure 37 Inflammatory papillary hyperplasia. The overlying stratified squamous epithelium shows acanthosis, hyperparakeratosis, and papillomatosis. There is an infiltrate of lymphocytes, plasma cells, macrophages, and neutrophils in the underlying hyperplastic, fibrovascular connective tissue.

C. Differential Diagnosis

The pseudoepitheliomatous hyperplasia may be so striking that invasive well-differentiated squamous carcinoma is entertained in the differential diagnosis by the pathologist. The clinical information is critical, but the lesion is well recognized by dentists and oral surgeons. No epithelial atypia is present in

inflammatory papillary hyperplasia, a very helpful finding. Nevertheless, before rendering a diagnosis of invasive well-differentiated squamous carcinoma from a palatal biopsy in a situation where there is limited clinical history, it may be of value to ascertain if the patient has a denture in place.

D. Treatment and Prognosis

Initial treatment usually involves directing the patient to remove the dentures when they sleep at night, in combination with topical antifungal therapy. If the papillae fail to resolve, surgical removal may be necessary (1,3,7).

XVIII. IRRITATION FIBROMA

Irritation fibroma is also known as focal fibrous hyperplasia, fibroma, fibrous nodule, and traumatic fibroma. Its etiology is the result of a chronic repair process that occurs in response to injury. Irritation fibromas are among the most common benign, reactive oral lesions with a reported occurrence rate from 0.2% to 0.7% of the population (1).

A. Clinical Features

The second decade of life is the most common age of presentation, but some authorities suggest that in their experience the lesions are more common in the fourth to sixth decade. Females are more commonly affected than males. The most common sites include buccal mucosa adjacent to the crowns of the teeth (the so-called bite line), the upper and lower labial mucosa, and the lateral borders of the tongue (2). These are the areas of oral mucosa which are most likely to be traumatized repeatedly by the adjacent dentition.

These fibrous lesions can present as a pedunculated nodule, but most frequently they are sessile (Fig. 38).



Figure 38 Irritation fibroma. A smooth-surfaced, ovoid, pedunculated or sessile, exophytic soft tissue nodule is noted in an area of chronic trauma, often involving buccal, glossal, or labial mucosa directly adjacent to the edges of the teeth.

The overlying mucosa is smooth and nonulcerated. They are typically light pink but in patients with dark skin, may be gray to blue-black in color. Irritation fibromas may range in size from several millimeters to as much as 2 cm or more but the majority are less than 1 to 1.5 cm.

B. Pathology

The low-power microscopic appearance of irritation fibromas mimics the clinical appearance, as they show a bosselated, pedunculated, or sessile appearance (Fig. 39). The surface is covered by a stratified squamous epithelium and the stroma is composed of collagen, fibroblasts, and varying amounts of chronic inflammatory cells. The stromal proliferation is unencapsulated and merges with the surrounding stroma. Usually the collagen is dense and tightly woven but may be loose. Dayan et al. have shown that the collagen fibers in irritation fibromas of long standing are arranged in a more organized, packed manner, whereas lesions of lesser duration are more disorganized (3).

C. Differential Diagnosis

Giant cell fibroma has been described as a separate entity, although it has some similarities to irritation fibroma. Some authors feel there is no need to separate these lesions from irritation fibroma, as the treatment is the same (4,5). Nevertheless, giant cell fibromas can also occur in areas of oral mucosa where chronic trauma is unlikely and irritation fibromas lack the giant, stellate cells seen in the former.

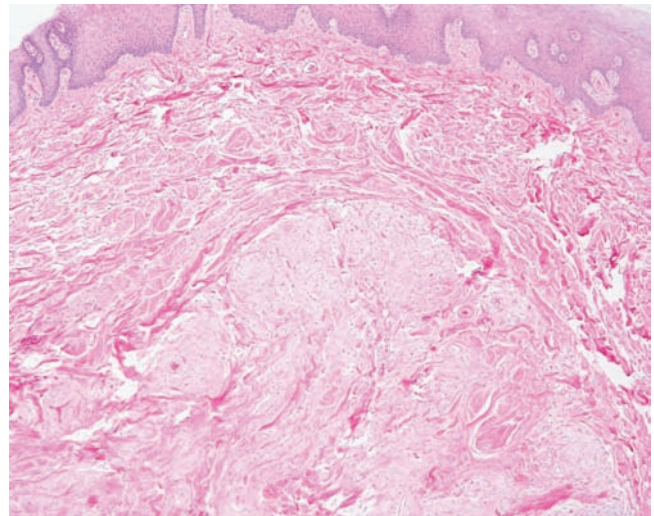


Figure 39 Irritation fibroma. The overlying stratified squamous epithelium can appear normal, focally hyperkeratotic, acanthotic, or ulcerated, depending on the clinical setting. The enlargement is the result of dense, reactive fibrocollagenous connective tissue in the superficial submucosa.

D. Treatment and Prognosis

Conservative surgical excision is the treatment of choice. Recurrence only occurs if repeated injury to the site continues.

XIX. GIANT CELL FIBROMA

Giant cell fibroma is a lesion that can clinically resemble irritation fibroma (focal fibrous hyperplasia) (1,2). Some authors do not separate the two entities, based partly on the overlapping clinical appearance and the similarities of treatment (3,4). However, there are some differences in the frequency of site involvement, in the average patient age at time of onset, and differences in histologic features (5). Importantly, giant cell fibroma does not appear to be convincingly associated with trauma.

A. Clinical Features

Giant cell fibroma is more common on the gingiva, with nearly half of patients having involvement of this site. The mandibular gingival is much more commonly affected than the maxillary gingiva at a 2:1 ratio. There is an equal sex distribution, and the process occurs predominantly in the first three decades. These features differ from those seen in irritation fibroma.

The clinical appearance is that of a bosselated or pedunculated lesion with a smooth mucosal surface (Fig. 40). Some lesions have a slightly papillary surface and may be confused clinically with papilloma in some cases. The size range is usually between 0.5 and 1.0 cm.

B. Pathology

The epithelium may show elongation of the rete, and the underlying connective tissue may be myxoid or

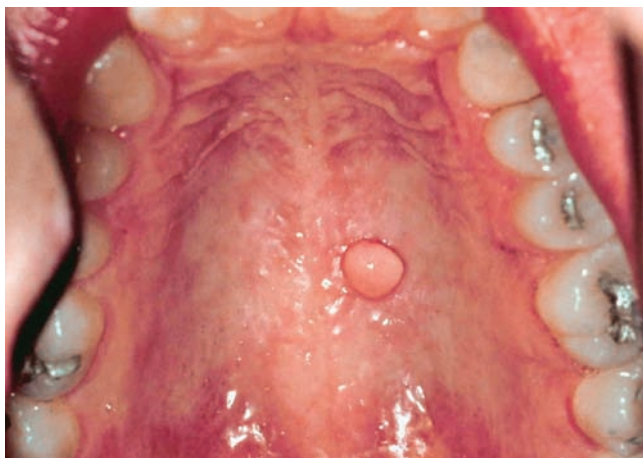


Figure 40 Giant cell fibroma. A smooth-surfaced, sessile or pedunculated, exophytic, soft tissue nodule. These nodules enlarge very slowly and are often identified only during oral health checkups.

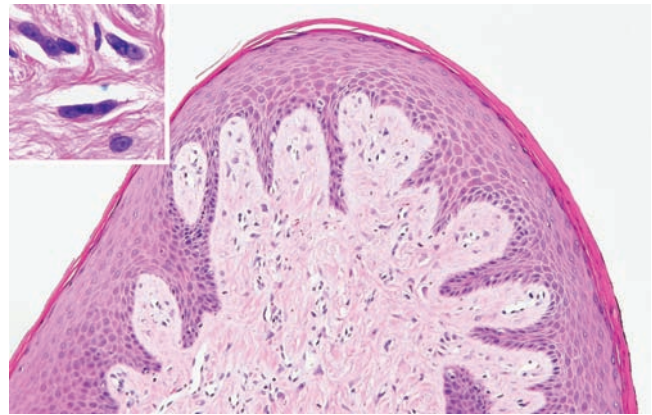


Figure 41 Giant cell fibroma. The surface of parakeratinized or nonkeratinized stratified squamous epithelium often shows reactive, pointed rete ridges extending down into a dense fibrocollagenous connective tissue core. Of note are numerous stellate and/or multinucleated fibroblasts, seen most often in the papillary submucosa (*inset*).

dense. The most striking finding histologically is the presence of stellate fibroblasts in the stroma. Many of these fibroblasts have multiple nuclei (Fig. 41). The collagen is characteristically dense and essentially identical to that found in an irritation fibroma (6–9).

C. Treatment

Giant cell fibromas are cured by local conservative excision and recurrences are rare.

XX. TONSILLITIS AND TONSILLAR HYPERPLASIA

A. Introduction

The tonsils are part of the lymphoid tissue making up Waldeyer's ring, which consists of the adenoids (pharyngeal tonsils), the palatine tonsils, and the lingual tonsils at the base of the tongue. The palatine tonsils are located in the tonsillar fossa between the palatoglossal and palatopharyngeal arches of the oropharynx (1). The palatoglossal muscle, the palatopharyngeal muscle, and the superior constrictor muscle form the ventral, dorsal, and lateral margins of the palatine tonsil. The pharyngobasilar fascia serves as the tonsil's capsule. Anomalies of tonsil development are rare, but occasionally foci of bone or cartilage can be found in fibrous tissue adjacent to or in the tonsil (2). The exposed surface of the tonsil has a cerebriform appearance due to the presence of crypts. The formation of deep tubular crypts is a characteristic of human palatine tonsils and pigs, but in some mammals crypts are lacking (1). In the human, each tonsil has 10 to 30 crypts, which increases the surface area. In the crypts, luminal antigens are taken up for specialized cells. The tonsils are located at the entryway of the

aerodigestive tract. They are exposed to many airborne and food antigens and have been considered as the first line of defense against pathogens (1,3). The epithelium lining the crypts is a specialized type of squamous epithelium and has a variable infiltration of lymphocytes. Investigators have found unique expression of tight junctions in the palatine tonsils and also suggest that the crypt epithelium may possess an epithelial barrier different from that of the surface epithelium (4).

The lymph nodes draining the tonsils are first the submandibular and then deep cervical, which explains the enlargement of these nodes during bouts of acute tonsillitis.

Tonsillitis may be caused by viruses or bacterial infection, but viral infections are likely more common. Bacterial infection may develop in the tonsil initially infected by virus.

The most common viral pathogens associated with tonsillitis include respiratory syncytial virus, echovirus, rhinovirus, adenovirus, influenza virus, and parainfluenza virus. EBV has also been implicated in recurrent episodes of tonsillitis (5–7).

Chronic tonsillitis and tonsillar hyperplasia appear related to bacterial infection and there is evidence that the presence of bacterial biofilms may explain the recurrent and chronic nature of tonsillitis (8–10). Immunologic alterations in the tonsil are also related to chronic tonsillitis. Investigators have found changes in the distribution of the antigen presenting dendritic cells within tonsils of children with and without chronic tonsillar disease (11). This may be due to pathogenic bacteria in the crypts of chronically inflamed tonsil (11).

Bacterial etiologies include group A *beta*-hemolytic streptococcus, *Haemophilus influenza*, and *Staphylococcus aureus* (12,13). However, other bacteria, including aerobe and anerobes, are important contributors to tonsillitis, and culture of tonsils removed for recurrent tonsillitis often show multiple organisms (14). Some investigators have suggested that while acute tonsillitis may be associated with group A *beta*-hemolytic streptococcus, Hemophilus groups are more likely to be involved in the pathogenesis of recurrent tonsillitis and tonsillar hyperplasia (14–16).

B. Clinical Features

Separating viral and bacterial etiology by symptomatology may be difficult, as sore throat is the most common symptom of tonsillitis in both viral and bacterial etiologies (13). Clinical features suggestive of viral etiology include cough, conjunctivitis, coryza, and diarrhea. Clinical features suggestive of bacterial tonsillitis include sore throat, fever, inflammation, exudates, and enlarged and tender anterior cervical lymph nodes. On physical examination, there is tonsillar and pharyngeal erythema. Palatal petechiae may be seen. Because branches of the glossopharyngeal and vagus nerves also innervate the ear, patients with tonsillitis may complain of ear pain (17).

Changes associated with enlarged tonsils from chronic tonsillitis may cause otitis media, Eustachian

tube dysfunction, voice changes, obstructive sleep apnea, and changes in facial growth (16). Children with large obstructing tonsils have a smaller oropharyngeal diameter compared with children with small tonsils (16).

Recurrent streptococcal tonsillitis has also been associated with pediatric autoimmune neuropsychiatric disorders (PANDAS) (18).

C. Pathology

Tonsillar tissue is at its largest size and immunologically most active during childhood, especially between 4 and 10 years but then decreases in size with age (16). Tonsillar size is said to be proportional to aerobic bacterial load and the absolute numbers of lymphoid cells (16). How chronic inflammation of the tonsil affects tonsillar size or histologic features is not entirely clear. Some studies suggest that *H. influenza* is highly associated with tonsillar hyperplasia (8). Controversy exists as to whether there are histopathologic differences in tonsils removed from children with either a history of recurrent tonsillitis or solely tonsillar hyperplasia without a clinical history of recurrent infections (19,20).

Because the tonsils are hematopoietic tissue, it may be difficult to define inflammation or “-itis” histologically. Tonsils are infrequently removed during “acute” tonsillitis unless there is concomitant peritonsillar abscess (see peritonsillar abscess). Tonsils removed for chronic or recurrent tonsillitis show lymphoid hyperplasia with large germinal centers (Fig. 42). Lymphocytes are seen normally in the epithelium but neutrophils are not and indicate, if prominent, “acute mucositis” (Fig. 43). The continuous antigenic stimulation of the tonsils has been termed a “physiologic inflammation,” and tonsillitis

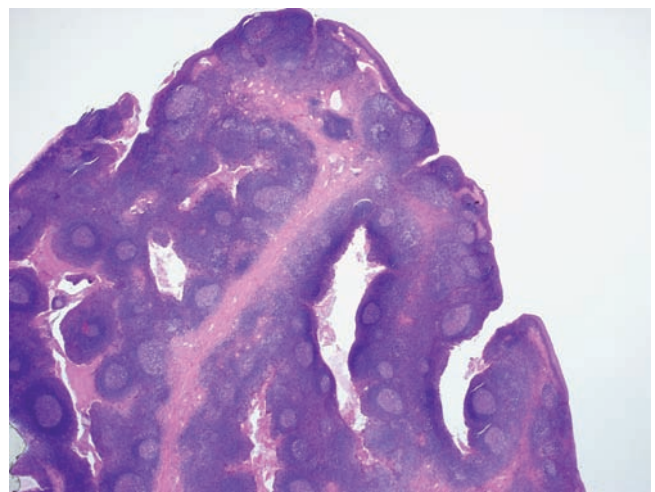


Figure 42 Tonsillar hyperplasia. Numerous hyperplastic lymphoid germinal centers of varying sizes are present. Tonsillar crypts with a minimal amount of desquamated surface epithelium are present.

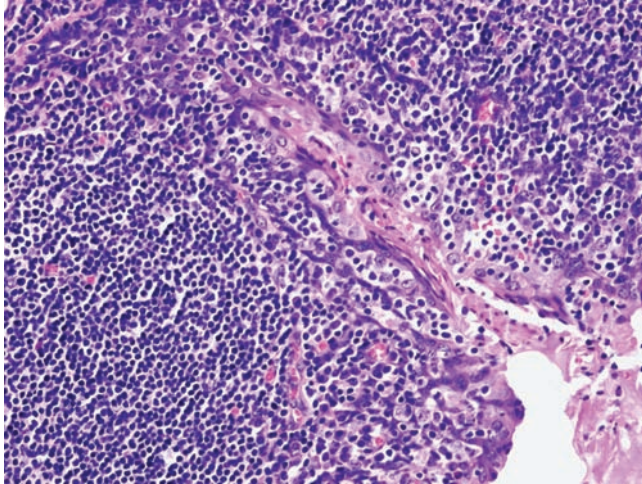


Figure 43 Tonsillar hyperplasia. The surface cryptal epithelium is infiltrated by lymphocytes, a normal finding.

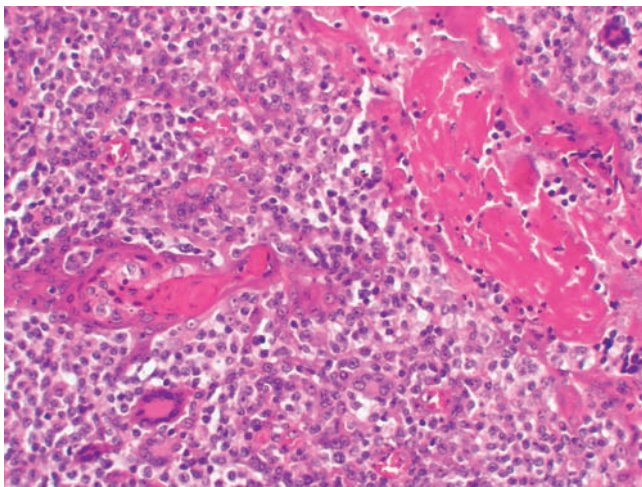


Figure 44 Giant cells in a tonsil from a patient with HIV infection. Multinucleated giant cells may be seen in tonsils in patients with HIV infection. The giant cells are often near the surface of the tonsil or near the cryptal epithelium. *Source:* Photograph courtesy of Dr. Leon Barnes, Pittsburgh, PA.

occurs if the pathogenic bacteria in the tonsillar tissue go beyond the functional limits of the resident lymphoid population. Actinomyces are normal inhabitants and can frequently be seen to form large colonies in the crypts. These should not be mistaken for disease. Giant cells may be seen in the epithelium of patients with HIV infection (Fig. 44) (21). Skeletal muscle is not uncommonly found in tonsil specimens surgically excised and is the result of extending the surgical excision to encompass the tonsillar capsule (22) (Fig. 45).

Complications of tonsillitis may be classified as nonsuppurative or suppurative. Nonsuppurative

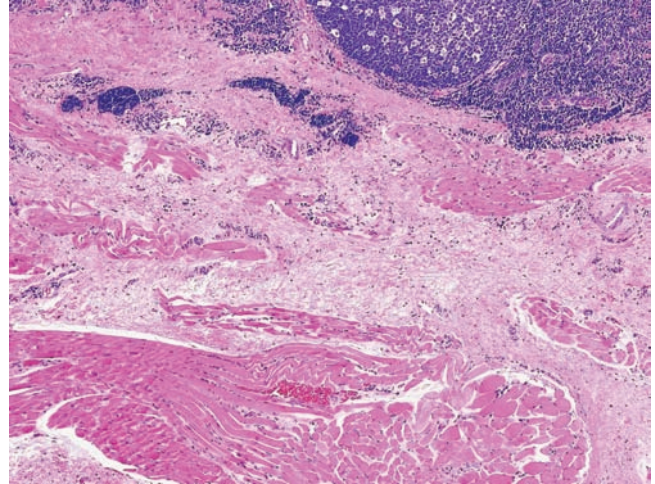


Figure 45 Tonsillar hyperplasia with skeletal muscle. This tonsillectomy specimen reveals abundant skeletal muscle. Skeletal muscle is not an unusual finding in tonsillectomy specimens when an extratonsillar capsular surgical procedure is performed.

complications include acute rheumatic fever, scarlet fever, and poststreptococcal glomerulonephritis. Suppurative complications include peritonsillar abscess, which may spread and result in parapharyngeal or retropharyngeal abscess (13). Lemierre's syndrome is characterized by septic thrombophlebitis of the internal jugular vein secondary to dissemination by contiguous spread of acute tonsillitis or pharyngitis (23). Spontaneous tonsillar hemorrhage of noniatrogenic causes has been reported in inflamed tonsil (24).

D. Treatment and Prognosis

Separating viral from bacterial causes of tonsillitis can be difficult. If the clinical findings suggest viral etiology, a number of authors suggest that additional diagnostic tests are not indicated (13,25). Most investigators emphasize the necessity of diagnostic testing for bacterial causes before treating with antibiotics, with rapid antigen detection testing the preferred laboratory test (25–30). Some guidelines support throat culture if the rapid antigen testing is negative, but that in adults, cultures are not suggested if the rapid antigen detection testing is negative (13). One main objective of antibiotic therapy is eradication of the organism from the pharynx, which is necessary for the prevention of acute rheumatic fever (31). Penicillin has been the standard treatment of streptococcal tonsillopharyngitis. However, in some studies, group A beta-hemolytic streptococcal resistance to penicillin occurs in up to 30% of patients and other antibiotics are required (13). Other agents have been suggested to be used for shorter courses, possibly with better compliance (31,32).

Studies using bacterial interference have also been carried out to prevent group A beta-hemolytic streptococcal-induced recurrent tonsillitis. In this method, patients are given *alpha-hemolytic streptococcus* to introduce bacteria that are not pathogenic but inhibit the growth of *beta-hemolytic streptococcus* (33).

The treatment of recurrent tonsillitis and tonsillar hyperplasia with tonsillectomy is controversial. Tonsillectomy is a procedure with a long history (34,35). Historically, the prevalence of tonsillectomy and adenoidectomy is cyclical (36). The rates of tonsillectomy and adenoidectomy vary markedly in various countries, with the pediatric rate of 19 per 10,000 children in Canada to 118 per 10,000 children in Northern Ireland in 1998 (37). Tonsillectomy is usually a procedure for children, but adults also have tonsils removed for a variety of reasons, including infections but also peritonsillar abscess, obstructive sleep apnea, as well as evaluation for suspected malignancy (38). Questions remain as to the efficacy of tonsillectomy for treating children with recurrent tonsillitis with proponents and opponents (12,39–43).

A long-standing concern by some is that removal of immunologically active organs in children may have a deleterious effect on the children's overall health. In a review of long-term studies by Paulussen et al., the authors could not find clinically significant alterations in cellular or humoral immunity in patients who had undergone tonsillectomy and adenoidectomy (3).

Some studies have suggested that tonsillectomy does little to decrease tonsillitis-related complications (44). Others have advocated against tonsillectomy if there is only mild symptoms of throat infections or adenotonsillar hypertrophy (43). Relative indications for tonsillectomy with adenoidectomy include upper airway obstruction, dysphagia or speech impairment, and halitosis, while recurrent or chronic pharyngotonsillitis, peritonsillar abscess, and streptococcal carrier state are indications for tonsillectomy but not adenoidectomy (45).

Whether tonsils should be examined microscopically by the pathologist is controversial. Some literature questions the value of histologic examination of all tonsils removed. Some suggest that tonsils removed in which there is no suspicion of malignancy, particularly tonsils removed for recurrent tonsillitis, or obstructive sleep apnea need not have histologic examination if the specimens are carefully examined grossly and the clinical findings are appropriate (38,46–51). Many pathology departments have set age-dependent criteria for omitting histologic examination of tonsils that show asymmetric enlargement or other abnormality ("gross only"). The most common patient ages chosen for which no histologic examination of tonsils is performed include 12, 16, and 21 years. In many instances, however, there is no individual pathology department-derived validation data that sets these age criteria for each institution. The safest policy is to examine all tonsils from all patients, regardless of age.

XXI. PERITONSILLAR ABSCESS

The space between the tonsillar pillars and the superior constrictor muscle on the one side and the tonsil on the other side is the peritonsillar space. This is the location of peritonsillar abscess. Importantly, the lateral pharyngeal space may be involved by direct extension of the abscess through the constrictor muscles (1). Peritonsillar abscess usually occurs in patients with recurrent tonsillitis or in those with chronic tonsillitis with inadequate treatment (2). Cervical necrotizing fasciitis has been reported following tonsillar infection (3). Clinically, there is unilateral swelling of the palate and anterior pillar with displacement of the tonsil downward (2). Examination of the pharynx is difficult because of trismus (1). Also, there is inability to control salivation because of the inability to swallow. Lateral plain radiographs may reveal thickening of soft tissues between the cervical vertebrae and the air column of the pharynx. Culture of the abscess often shows both anaerobic and aerobic bacteria (4). Because of the mixed flora, some investigators have suggested that antibiotics to cover anaerobic bacteria be used initially (4). If the abscess spreads into the parapharyngeal space, the process could also extend down the carotid sheath and into the mediastinum. Retropharyngeal abscesses likely arise because of the abscess forming in lymph nodes in the retropharyngeal space (2). Peritonsillar cellulitis is treated medically with antibiotics. Needle aspiration and incision and drainage are required for treatment of peritonsillar abscess usually followed by tonsillectomy later, although there may be indications for immediate tonsillectomy (5).

XXII. ADENOID HYPERPLASIA

Similar to the tonsil, the adenoids, also known as the pharyngeal tonsils, are part of Waldeyer's ring. The adenoids are also situated at the entrance of the nasopharynx, and their afflictions are similar to those of the tonsil. Anatomic differences exist, however, in that the adenoids do not have a peripheral capsule (fascia), as does the tonsil. The adenoids are covered by respiratory-type epithelium in children, although the adenoids of adults may have a partial covering by squamous epithelium. The adenoids likely have active immune function. Immunologic functional studies have revealed a variety of immune processing in the adenoids such as toll-like receptor expression (1).

The adenoids cause problems because of inflammation and lymphoid hyperplasia. Numerous adverse effects of enlarged adenoids have been described in the literature and rationales for surgical removal have been given. The conclusions are controversial. Chronic nasal obstruction due to increased adenoidal size is thought by some to be associated with obstructive sleep apnea, eustachian tube dysfunction and otitis media, and abnormal facial growth (2,3). Adenoidal hyperplasia may lead to nasal obstruction, with investigations showing that nasal obstruction is likely secondary to an absolute increase in adenoid size rather than a relatively smaller nasopharynx (4).

While some have suggested that abnormal facial and dental development have a relation to enlarged adenoids (adenoidal facies), not all investigators have found this to be true (4).

Increased stratified squamous epithelium and decreased ciliated epithelium is seen in adenoids from patients with otitis media, and the investing epithelial cell layer extends more deeply into the lymphoid crypts in patients with otitis media (5). This epithelium appears to lack antigen-transporting cells and would support an abnormality of the antigen-trapping systems that is seen in adenoidal hyperplasia (6).

The role of enlarged adenoids in otitis media with effusion is not completely clear. Besides potential obstruction of the Eustachian tube by enlarged adenoidal tissue, the inflammatory-induced metaplasia of the nonciliated surface may impair mucociliary drainage (7). Many authors, however, suggest that adenoid enlargement is unrelated to otitis media and that there is no difference in adenoid size between children with or without otitis media with effusion (2,5,8). Most authors agree that the adenoids may have an important role in the cause of otitis media with effusion by serving as a reservoir for bacteria (5). *H. influenza* is often cultured more frequently in adenoid specimens from patients who have otitis media with effusion. This is a reason that some authors recommend that children who have bacterial otitis media and nasal obstruction should undergo adenoidectomy to remove the chronically infected tissue (9).

Studies have reported adenoidal hypertrophy occurring in adults with HIV infection (10). Adenotonsillar hyperplasia may be a precursor to EBV-related lymphoid hyperplasia and posttransplant lymphoproliferative disease (11).

A. Pathology

The adenoids are prominent in children but begin to shrink in size at puberty and are often small and fibrotic in adults. The prominence is due to lymphoid proliferation, which decreases with age (7). Mucosal and submucosal lymphocytic infiltration are normally present in the adenoid and should not be construed as chronic inflammation. The adenoids usually show follicular lymphoid hyperplasia with enlarged germinal centers. Tingible body macrophages are commonly seen. Interestingly, neutrophils are not usually seen. In children, the epithelial surface may be transformed from a ciliated-type to a stratified squamous epithelium extending into the adenoidal lymphoid tissue (6). In adults, the adenoids may show significant fibrosis. Epstein-Barr infection may cause the adenoids, like the tonsils, to show marked immunoblastic reactions with Reed-Sternberg-like cells.

B. Treatment

Adenoidectomy is often an added procedure to tonsillectomy but may add complications. Besides increasing operative time, operative blood loss is

increased and because the adenoids normally tend to decrease in size as puberty is reached, removal in older children is controversial (12). While some clinicians believe that symptoms due to enlarged adenoids recur because of regrowth of the adenoid tissue, others suggest that adenoidal tissue rarely, if ever, proliferate sufficiently after resection to cause symptoms of nasal obstruction (13).

Adenoidectomy has been suggested to be of benefit in patients with otitis media and chronic nasal obstruction and is a common indication for adenoidectomy for some surgeons (8). Some authors suggest that there are specific indications for tonsillectomy alone, tonsillectomy combined with adenoidectomy, and adenoidectomy alone. Otitis media and recurrent or chronic rhinosinusitis or adenoiditis are indications for adenoidectomy but not tonsillectomy (3,14). Children with sleep apnea may benefit from tonsillectomy and adenoidectomy (14). Adenotonsillectomy in children with mild symptoms of throat infections or adenotonsillar hyperplasia may not have a benefit from surgical removal (15).

XXIII. OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea is defined as obstruction, either complete or partial, of the upper airway during sleep, and when combined with daytime sleep symptoms, this condition is termed "obstructive sleep apnea syndrome" (1,2). Obstructive sleep apnea is more common in males until patients reach their fourth and fifth decade, when the male-to-female ratio drops from 3:1 to 1:1. Its prevalence is reported to be up to 5% in the Western world, and sleep apnea is thought to affect 20 million Americans. The peak age for obstructive sleep apnea in children due to tonsil and adenoid hyperplasia is three to six years, although it may occur in younger children, including infants (3). Children with Down syndrome are also thought to be at increased risk of obstructive sleep apnea from tonsillar and adenoid hyperplasia (4). Besides hyperplasia due to bacterial and common viral causes, obstructive sleep apnea has also occurred secondary to EBV-induced lymphoid hyperplasia of the tonsil and adenoid following transplantation (5).

Obstructive sleep apnea is considered to be multifactorial and may even have a genetic basis with complex interactions of neural, hormonal, and structural abnormalities (2,6). Although there is variability in the dimensions of airways in normal adults, most investigators believe patients with obstructive sleep apnea have narrower airways than normal.

In adults, obesity is probably the greatest risk factor. Regional fat distribution has also been shown to have a genetic component and may be more important than overall obesity. However, not all patients with obstructive sleep apnea are overweight (2). Obstructive sleep-disordered breathing occurs because of numerous other factors, including increased adipose tissue (parapharyngeal fat pad) alterations in craniofacial structures, reduction in mandibular size, disease of the paranasal sinuses, tonsil and adenoid

hyperplasia, hypertrophy of the soft palate and uvula, low-set soft palate, micrognathia, macroglossia, and tongue root depression (6–8). Narrowing or obstruction of the middle pharynx and hypopharynx is more marked in patients with obstructive sleep apnea than in normal patients and is particularly marked during sleep (7).

Obvious genetic abnormalities such as Pierre-Robin syndrome, Down syndrome, Apert syndrome, Treacher-Collins syndrome, and achondroplasia are associated with patients who have sleep-disordered breathing (6). Obstructive sleep apnea is also reported clustered in families, and some case reports suggest autosomal dominant inheritance.

A. Clinical Features

The cardinal symptom of obstructive sleep apnea is excessive daytime sleepiness (9). Other symptoms include unrefreshing sleep or chronic fatigue (1). Snoring is often a common complaint, as is awakening with a smothering sensation or gasping, awakening with a headache or dry throat, and restless sleep. Other medical problems are associated with obstructive sleep apnea and include both systemic and pulmonary hypertension, coronary artery disease, cardiac arrhythmias, diabetes, and decreased neurocognitive functions. Gastroesophageal reflux, impotence, and depression are also associated with obstructive sleep apnea, as are motor vehicle accidents, poor work performance, and occupational accidents associated with obstructive sleep apnea (1,2,10).

Infants may have disturbed sleep with repetitive crying and snoring. Children aged between one and three years may have snoring but also aggressive daytime behavior. An overnight sleep study (polysomnography) is considered to be of great value in diagnosing obstructive sleep apnea. Polysomnography can help determine the apnea-hypoxia index, determined by the average number of apneic and hypopneic episodes per hour of sleep.

B. Pathology

Tonsil and adenoid hyperplasia is said to be a leading cause of obstructive sleep apnea in children. The tonsils and adenoids do not have specific features that set them apart from the hyperplastic tissue seen in patients without obstructive sleep apnea. Both children and adults may undergo uvulopalatoplasty to enlarge the airway and help prevent it from collapsing. Uvulopalatoplasty specimens do not generally show any striking histologic changes (Fig. 46).

C. Treatment and Prognosis

Sometimes simple therapies may help alleviate milder symptoms of obstructive sleep apnea. Encouraging the patient to sleep on their side, lose weight if obese, and to refrain from alcohol before bedtime may help. Other therapies include continuous positive airway pressure (CPAP) and oral appliances used

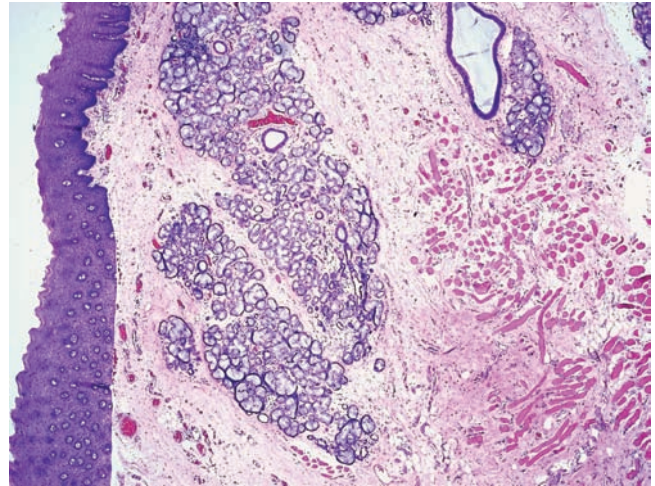


Figure 46 Uvula and palatal tissue from uvulopalatoplasty. The overlying epithelium and submucosal glands and skeletal muscle are normal in histologic appearance.

during sleep. Surgical therapy (uvulopalatoplasty) is aimed at enlarging the posterior airway space and reducing the ability of the airway to collapse (2).

XXIV. LOBULAR CAPILLARY HEMANGIOMA (PYOGENIC GRANULOMA)

Lobular capillary hemangioma is a common lesion of the oral cavity that has now been considered by some to be synonymous with pyogenic granuloma, although some authors believe the two processes are distinct entities (1–3). Epulis granulomatosa is a designation used to describe lesions that appear as pyogenic granulomas that arise in healing extraction tooth sockets.

Lobular capillary hemangioma is a smooth or lobulated mass that may be either sessile or pedunculated. The tissue may histologically resemble granulation tissue or, if there is minimal inflammation, a hemangioma. Etiologies include lip biting, trauma, tissue edges of restorations, and tooth extraction sites. Rapid growth is not uncommon. Tie2, a human endothelial receptor tyrosine kinase, has been implicated in the development of lobular capillary hemangioma (4). Pyogenic granuloma usually affects children and young adults, but they may occur at any age, including infancy (5). In a study of patients 65 years and older, pyogenic granuloma was seen in 0.7% (6).

A. Clinical Features

Lobular capillary hemangioma or pyogenic granuloma varies from pink to red to purple and may range from several millimeters to several centimeters. These tumors often arise on the gingiva, particularly the anterior maxillary gingiva but may occur anywhere in the oral cavity, including the lips, tongue, and buccal mucosa (Fig. 47). They often have a rapid



Figure 47 Lobular capillary hemangioma or pyogenic granuloma. An erythematous, sessile or pedunculated, easily bleeding soft tissue enlargement. They can occur anywhere, but when they involve the oral cavity, they are most often noted in areas of chronic inflammation adjacent to teeth. They can grow rapidly, often alarming the patient and clinician.

growth rate mimicking aggressive malignant vascular neoplasms. The majority of patients are female and thus the role of estrogens and progesterone may well have at least a partial etiologic role. The development of these lesions during pregnancy has given rise to the term “pregnancy tumor” or “granuloma gravidarum” (7). In this specialized clinical setting, the tumors are initially seen in the first trimester and increase in frequency as the pregnancy continues up to around the sixth or seventh month of gestation, suggesting a correlation with hormone levels. Interestingly, after delivery, these lesions may regress on their own, with only a fibrous process remaining.

The clinical differential diagnosis includes other vascular lesions, including angiosarcoma or vascular metastatic lesions (8,9). Bacillary angiomatosis mimicking pyogenic granuloma has also been reported (10,11).

B. Pathology

Histologically, lobular capillary hemangiomas show a spectrum or evolution of changes as they mature. Initially the appearance is that of primarily vascular proliferation and inflammation, which resembles granulation tissue. The vessels are arranged in a lobular pattern often with central radiation to a more central point at the base of the lesion. In early lesions, the surface may be ulcerated, and some authors use the term “pyogenic granuloma” in this setting. There is a variable amount of inflammatory infiltrate and, when present, may be neutrophilic, lymphoplasmacytic, or mixed. The inflammatory component is usually more pronounced near the surface. Over time, the inflammatory component diminishes and the endothelial cell proliferation, once marked at the lesions

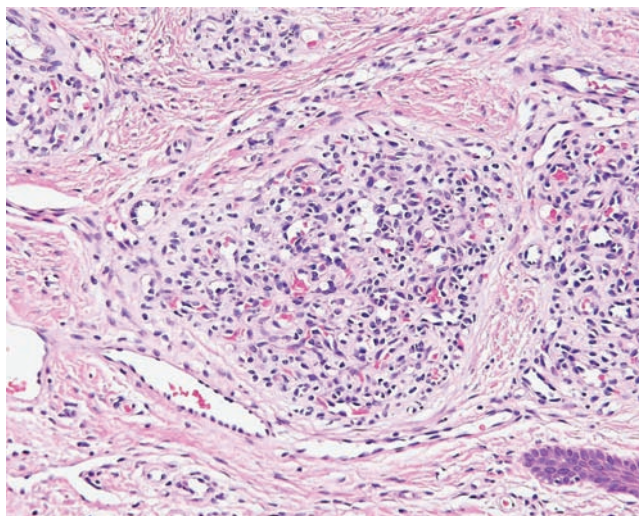


Figure 48 Lobular capillary hemangioma or pyogenic granuloma. The overlying epithelium is often normal but can be focally ulcerated. The underlying fibrovascular connective tissue shows numerous thin-walled vascular channels, often arranged in lobules just subjacent to the surface epithelium. Most oral lesions show a mixed infiltrate of lymphocytes, plasma cells, and neutrophils. The multifocal lesions of so-called pregnancy gingivitis are often microscopically identical to oral lobular capillary hemangioma or pyogenic granuloma.

inception, decreases with shrinkage of the endothelial cell nuclei. The end stages of the lesion result in a collection of small vessels in a lobular pattern with minimal inflammation in a more prominent fibrous stroma (Fig. 48).

C. Differential Diagnosis

The lobular growth pattern is a key feature and helps differentiate it from other vascular neoplasms. Mitoses are frequent in early lesions and may even exhibit more mitoses than low-grade angiosarcomas. Atypical mitoses, however, are not seen in lobular capillary hemangiomas. Importantly, lobular capillary hemangiomas do not show a diffuse or widely infiltrative growth pattern.

D. Treatment and Prognosis

Conservative surgical therapy is adequate for these benign lesions. Some authors suggest that pyogenic granulomas that arise during pregnancy should not be excised until some time after delivery, as they may spontaneously involute.

XXV. CROHN DISEASE

Crohn disease is a chronic inflammatory process that most frequently involves the terminal ileum and colon but may also affect the small bowel and upper

digestive tract, including the oral cavity. Involvement of numerous extragastrointestinal sites has also been reported, including the eye, skin, and joints. Multiple oral mucosal sites of involvement have been reported, including the tonsillar region (1,2). The prevalence of Crohn disease has been increasing over the last several decades (3). Intraoral lesions may be seen in 4% to 16% of patients with Crohn disease and, interestingly, lesions have been reported to frequently precede the development of intestinal inflammation (4). No cause has yet been proven for Crohn disease (5).

Oral Crohn is marked by a male predominance and a young age at onset. There is a 3:1 male predominance in the 16- to 30-year-old group. In young patients who have recurrent painful intraoral ulcerative lesions with no other signs, Crohn disease should be excluded. The course of oral Crohn disease may be very protracted (6). Oral findings appear to be more common in patients with colonic disease than ileocolonic or ileal disease (7).

A. Clinical Features

The clinical appearances are varied and include thickening and redness of the gingiva, cobblestone appearance of the buccal mucosa, diffuse labial swelling, and epithelial tags (8–11). Aphthous ulcerations are present in 20% of patients, but this is not significantly higher than in the general population (9). Linear ulcers, similar to those seen in the gastrointestinal tract, may be present. Midline lip fissuring, gingivitis, and angular cheilitis are also reported (12). Patients with oral Crohn disease also have a higher prevalence of anal and esophageal involvement, suggesting that these patients have disease that is more likely to target squamous epithelium (6). Buccal space infection with salivary duct fistula has been reported with Crohn disease (13). Crohn disease is also associated with poor dental health, including a higher risk of dental caries, particularly in patients with active disease (14).

B. Pathology

Histologically, the inflammatory reaction shows intense, frequently perivascular, lymphocytic infiltration with follicle formation in addition to noncaseating granulomas (7) (Fig. 49). The granulomas may or may not be present in the superficial submucosa. Granulomatous inflammation of minor salivary gland ducts has also been reported (15). Some studies suggest that granulomas are more commonly found in the oral biopsies than in the intestinal biopsies of patients with Crohn disease.

C. Differential Diagnosis

Clinically, the differential for oral Crohn disease includes cheilitis glandularis, infectious agents (including fungal, bacterial, and mycobacterial), sarcoid, nonspecific aphthous ulcers, allergies, foreign body reaction, and orofacial granulomatosis (5,8,9,12,16–19). If followed for a sufficient time, some patients with

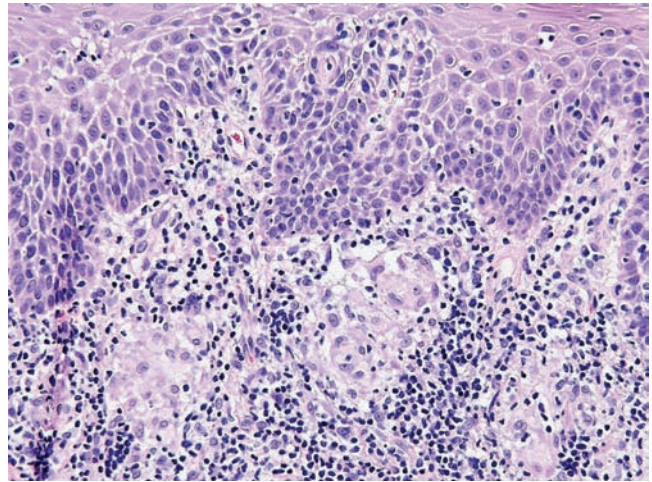


Figure 49 Crohn disease. The overlying epithelium shows focal areas of atrophy, often to the point of ulceration. As with lower gastrointestinal lesions, the submucosa will show foci of chronic nonnecrotizing, granulomatous inflammation.

the diagnosis of orofacial granulomatosis will develop signs of Crohn disease (20).

D. Treatment

Immunosuppressive therapy with steroids and other drugs have been reported to be of value in the treatment of oral lesions of Crohn disease. Exacerbations of oral lesions usually coincide with exacerbations of colonic inflammation.

XXVI. ECTOPIC THYROID

Ectopic thyroid is thyroid tissue usually found along the course of the thyroglossal duct, in the tongue, and in lymph nodes of the neck. Other sites include the parapharyngeal space, parotid gland, submandibular gland, oropharynx, mediastinum, porta hepatis, breast, uterus, duodenum, gallbladder, vagina, adrenal, pancreas, axilla, heart, and dermis (1–7).

The following discussion concerns only lingual thyroid, thyroid inclusions in cervical lymph nodes, and thyroid tissue in nonlymphoid tissue of the head and neck.

A. Lingual Thyroid

Thyroid tissue located in the tongue is a congenital abnormality and is due to the failure of the thyroid gland to descend from its embryologic site of origin at the foramen cecum to its usual pretracheal position (8–10). The pathogenesis is unclear, but some have speculated that maternal antithyroid immunoglobulin may stop thyroid gland descent.

Clinical manifestations of lingual thyroid are rare, but in an autopsy study of 184 cadaver tongues,

9.8% had thyroid inclusions (8). Hypothyroidism is commonly seen in patients with lingual thyroid, and some have speculated that lingual thyroid is a physiologic response by small thyroid remnants in the tongue to low thyroid levels. Some have suggested that lingual thyroid becomes more prominent or is brought to clinical attention under times of stress, when the thyroid hormone normally produced is insufficient and the resulting hypertrophy causes symptomatic enlargement because of increases in thyroid-stimulating hormone. Hyperthyroidism has been reported in patients with lingual thyroid (11). It is important to realize that 70% of patients with lingual thyroid sufficiently prominent to be clinically recognized have no other thyroid tissue and thus become hypothyroid after excision (12).

Clinical Features

Lingual thyroid is reported to have a bimodal age distribution, with peaks at ages 12 and 50 (12). Although lingual thyroid is congenital, most patients present with symptoms in the third decade with ages ranging from infancy to the eighth decade. Lingual thyroid is much more frequent in females than males (13). Airway intubation failure due to obstruction in patients with lingual thyroid is well recognized (14).

In those cases where there are symptoms, the patients complain of sensations of a foreign body in the throat, dysphonia, dysphagia, or hemoptysis (9,15). Lingual thyroid may vary in size from several millimeters to several centimeters and is located in the midline of the base of the tongue, usually between the circumvallate papillae and the epiglottis (Fig. 50). A radioactive thyroid scan is a good method to diagnose the process but fine needle aspiration has also been used (2,15,16). Usually more anatomically refined imaging studies such as computed tomography or magnetic resonance are required to define the size of the tissue.



Figure 50 Lingual thyroid. A smooth, sessile, vascular nodule, usually noted on the dorsal tongue just anterior to the circumvallate papillae.

Pathology

Histologically, the thyroid tissue appears normal. The thyroid tissue may be circumscribed but is usually interdigitating with skeletal muscle and minor salivary gland tissues.

Treatment and Prognosis

Small lesions without symptoms usually require no therapy. Treatment may include the administration of thyroid hormone with possible regression in the size of the tissue (17). Ablation with radioactive materials is another potential method of treatment (14).

Indications for surgery include airway obstruction, dysphagia, obstructive sleep apnea, or repeated significant hemorrhage (18). Rarely, thyroid carcinoma may arise in lingual thyroid (19). Angiography may play an important role in the preoperative assessment of patients who are candidates for surgical therapy, as there may be anatomic variations in the blood supply to lingual thyroid (10,17).

B. Benign Thyroid Inclusions in a Lymph Node

“Lateral aberrant thyroid tissue” is a term that has been employed to imply a number of situations in which thyroid tissue is found outside its normal location. Most commonly, this term has implied thyroid follicles in a cervical lymph node. To some, this finding has always meant that the tissue was metastatic from a thyroid primary. However, benign thyroid follicles may exist in a lymph node with no coexistent thyroid malignancy.

The unexpected presence of thyroid epithelial cells in lymph nodes has caused significant controversy over the implication and therapeutic management of the patient (1). The clinical situation most frequently arises when thyroid epithelium is found in lymph nodes that are removed in therapy for a nonthyroid malignancy, such as squamous cell carcinomas. In the opinion of some authors, almost all these “inclusions” represent metastatic thyroid carcinoma (2,3). However, other authors do not embrace this opinion (4-6).

In an autopsy study, microscopically normal thyroid follicles were found in cervical lymph nodes in 5 of 106 autopsies, but no thyroid carcinomas were found in the ipsilateral thyroid gland (7). In another study, to determine the prevalence of occult metastatic thyroid carcinoma or other unexpected malignancy Ansari-Lari et al. studied 1337 patients who underwent cervical lymphadenectomy during a 17-year period (8). In 10 patients (0.7%), the lymph nodes contained cells that were histologically diagnosed as papillary thyroid carcinoma. In 11 patients (0.8%), there were lymph nodes with what were histologically considered to be benign thyroid inclusions (9 of the 11 patients) or psammoma bodies (2 of the 11 patients). Four of these eleven patients underwent thyroidectomy, but no thyroid cancer was found on the ipsilateral side.

Leon et al. reported that the incidence of unsuspected thyroid tissue in lymph nodes of patients with head and neck carcinomas treated with neck dissection was 1.5%. Lymph node metastases from a papillary carcinoma as well as benign thyroid inclusion were found (9). These authors suggested that thyroid tissue found incidentally in cervical lymph nodes removed for other head and neck cancers did not necessarily indicate the need for additional therapy. A clonality study of benign-appearing thyroid follicles in lymph nodes was reported to show that the tissue was polyclonal (10).

Pathology

Benign inclusions should be represented by only a few small follicles located in or immediately beneath the lymph node capsule (11) (Fig. 51). These should not have cleared nuclei or contain grooves, folds, or inclusions nor show papillary formation (Fig. 52).

Rosai et al. suggested that a diagnosis of metastatic carcinoma be made in any case in which the thyroid tissue has replaced one-third or more of the node or in which several nodes are affected (11).

Treatment

No generic all-encompassing therapeutic approach is possible. From a number of studies, it appears that patients with small inclusions of thyroid tissue without features of papillary carcinoma do not always require thyroidectomy. Most authorities do suggest clinical examination of the thyroid and radiographic or ultrasonic imaging to determine if thyroid masses are present (1). Some studies suggest that even in patients with histologic features of papillary thyroid carcinoma, thyroidectomy does not always “find” a neoplasm in the gland. Further, in those patients with primary thyroid carcinomas found after initial

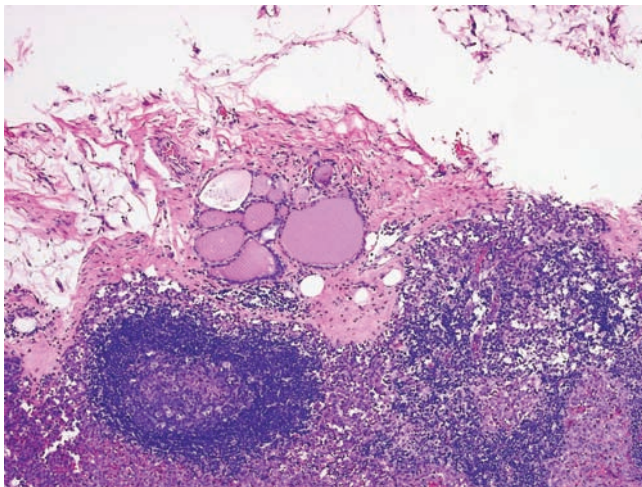


Figure 51 Benign thyroid inclusions in lymph node. A small cluster of thyroid follicles is present in the subcapsular region of the lymph node. No papillary structures are evident.

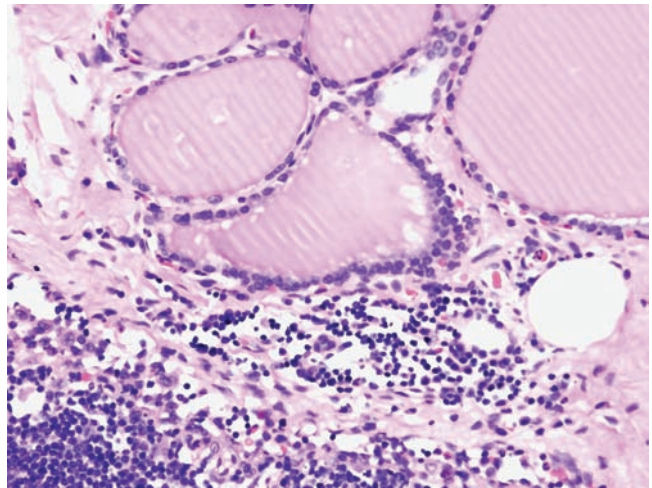


Figure 52 Benign thyroid inclusions in lymph node. Thyroid follicles show no nuclear inclusions, clearing, grooves, or nuclear overlap.

unsuspected presentation in cervical lymph nodes, the thyroid carcinoma is often indolent (3,8,12). Careful tailoring of diagnostic and therapeutic options is required.

C. Ectopic Benign Thyroid Tissue in Nonlymphoid Tissues of the Head and Neck

Besides being found in the tongue or cervical lymph nodes, benign thyroid tissue may be found in other locales of the head and neck. The thyroid tissue may be incidentally found or may present as a mass. Thyroid may be seen that is in the midline, outside of the tissues of the tongue, along the track of the normal descent of the thyroid. In the midline this tissue is most commonly seen in the region of the thyroglossal duct (1). The trachea and laryngo-tracheal area are also known to harbor thyroid tissue, and in this location the tissue may grow to such a size as to obstruct the airway (2–4). Patients with ectopic thyroid in the neck may also present with thyrotoxicosis, in a manner similar to those patients with lingual thyroid that becomes hyperfunctional (5,6). Nonmidline sites may also contain thyroid tissue, including the submandibular gland, parotid, skin, carotid sheath, and retropharyngeal and lateral oropharyngeal spaces (7–13).

In some cases, thyroid may be found in patients that have had prior surgery in the neck and thus may represent unintentionally implanted thyroid tissue (14).

Clinical Features

It is important to realize that in some patients, the ectopic thyroid tissue may be the only functioning thyroid tissue. This may suggest that use of

preoperative techniques, such as fine needle aspiration, be performed prior to total surgical excision of a mass of unknown etiology (15).

Pathology

The thyroid tissue in these ectopic locations appears as normal thyroid tissue, although in hyperfunctional states the appearances are those seen in Graves disease. The ectopic thyroid tissue should not have histologic or cytologic characteristics of thyroid carcinoma.

Treatment and Prognosis

Large masses are best treated by excision; however, consideration must be given to the fact that the excised tissue may represent the patient's only thyroid.

REFERENCES

I. FORDYCE GRANULES

- Halperin V, Kolas S, Jefferis KR, et al. The occurrence of Fordyce spots, benign migratory glossitis, median rhomboid glossitis, and fissured tongue in 2,478 dental patients. *Oral Surg Oral Med Oral Pathol* 1953; 6(9):1072-1077.
- Flinck A, Paludan A, Matsson L, et al. Oral findings in a group of newborn Swedish children. *Int J Paediatr Dent* 1994; 4(2):67-73.
- Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. *Dent Oral Epidemiol* 2000; 28:390-398.
- Leider AS, Lucas JW, Eversole LR. Sebaceous choristoma of the thyroglossal duct. *Oral Surg Oral Med Oral Pathol* 1977; 44(2):261-266.
- Levinson AW, Jakobiec FA, Reifler DM, et al. Ectopic epibulbar Fordyce nodules in a buccal mucous membrane graft. *Am J Ophthalmol* 1985; 100:724-727.
- Marback EF, Gonzaga RL, Rigueiro MP, et al. Fordyce nodules in a buccal membrane graft to the ocular surface. *Ophthalm Plast Reconstr Surg* 2002; 18(4):308-309.
- Rhodus NL. An actively secreting Fordyce granule. *Clin Prev Dent* 1986; 8(2):24-26.
- Daley TD. Intraoral sebaceous hyperplasia. *Oral Surg Oral Med Oral Pathol* 1992; 74:343-347.
- Alwai F, Siddiqui A. Sebaceous carcinoma of the oral mucosa: case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99:79-84.
- Dilley DC, Siegel MA, Budnick S. Diagnosing and treating common oral pathologies. *Pediatr Clin North Am* 1991; 38(5):1227-1264.
- Monk BE. Fordyce spots responding to isotretinoin therapy. *Br J Dermatol* 1993; 129(3):355.

II. WHITE SPONGE NEVUS

- Cannon AB. White sponge nevus of the mucosa (naevus spongiosus albus mucosae). *Arch Derm Syph* 1935; 31:365-370.
- Gorlin RJ, Sedano HO. Oral manifestations of systemic genetic disorders. *Postgrad Med* 1971; 49(4):155-160.
- Richard G, De Laurenzi V, Didona B, et al. Keratin 13 point mutation underlies the hereditary mucosal epithelial disorder white sponge nevus. *Nat Genet* 1995; 11(4):453-455.

- McLean WHI, Lane EB. Intermediate filaments in disease. *Curr Opin Cell Biol* 1995; 7(1):118-125.
- Banoczy J, Sugar L, Frithiof L. White sponge nevus: leukoedema exfoliativum mucosae oris. *Swed Dent J* 1973; 66:481-493.
- Krajewska IA, Moore L, Brown JH. White sponge nevus presenting in the esophagus - case report and literature review. *Pathology* 1992; 24:112-115.
- Nichols GE, Cooper PH, Underwood PB Jr., et al. White sponge nevus. *Obstet Gynecol* 1990; 76(3 pt 2):545-548.
- Jorgenson RJ, Levin S. White sponge nevus. *Arch Dermatol* 1981; 117:73-76.
- Whitten JB. The electron microscopic examination of congenital keratosis of the oral mucous membranes. *Oral Surg Oral Med Oral Pathol* 1970; 29(1):69-84.
- Chao SC, Tsai YM, Yang MH, et al. A novel mutation in the keratin 4 gene causing white sponge naevus. *Br J Dermatol* 2003; 148(6):1125-1128.
- Rugg EL, Magee GJ, Wilson NJ. Identification of two novel mutations in keratin 13 as the cause of white sponge naevus. *Oral Dis* 1999; 5:321-324.
- Rugg EL, McLean WHI, Allison WE. A mutation in the mucosal keratin K4 is associated with oral white sponge nevus. *Nat Genet* 1995; 11(4):450-452.
- Terrinoni A, Rugg EL, Lane EB, et al. A novel mutation in the keratin 13 gene causing oral white sponge nevus. *J Dent Res* 2001; 80(3):919-923.

III. ORAL MELANOCYTIC NEVI

- Buchner A, Merrell PW, Carpenter WM. Relative frequency of solitary melanocytic lesions of the oral mucosa. *J Oral Pathol Med* 2004; 33:550-557.
- Buchner A, Hansen LS. Pigmented nevi of the oral mucosa: a clinicopathologic study of 36 new cases and review of 155 cases from the literature. Part I: A clinicopathologic study of 36 new cases. *Oral Surg Oral Med Oral Pathol* 1987; 63:566-572.
- Allen CM, Pellegrini A. Probable congenital melanocytic nevus of the oral mucosa: case report. *Pediatr Dermatol* 1995; 12(2):145-148.
- Biesbrock AR, Aguirre A. Multiple focal pigmented lesions in the maxillary tuberosity and hard palate: a unique display of intraoral junctional nevi. *J Periodontol* 1992; 63:718-721.
- Fistarkol SK, Itin PH. Plaque-type blue nevus of the oral cavity. *Dermatology* 2005; 211(3):224-233.
- Pinto A, Raghavendra S, Lee R, et al. Epithelioid blue nevus of the oral mucosa: a rare histologic variant. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96:429-436.
- Ficarra G, Hansen LS, Engebretsen S, et al. Combined nevi of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 1987; 63:196-201.
- Eisen D, Voorhees JJ. Oral melanoma and other pigmented lesions of the oral cavity. *J Am Acad Dermatol* 1991; 24:527-537.
- Leston JMS, Garcia JV, Santos AA, et al. Dark oral lesions: differential diagnosis with oral melanoma. *Cutis* 1998; 61(5):279-282.
- Cicek Y. The normal and pathological pigmentation of oral mucous membrane: a review. *J Contemp Dent Pract* 2003; 4(3):76-86.
- Gaeta GM, Satriano RA, Baroni A. Oral pigmented lesions. *Clin Dermatol* 2002; 20(3):286-288.
- Kaugars GE, Heise AP, Riley WT, et al. Oral melanotic macules. *Oral Surg Oral Med Oral Pathol* 1993; 76:59-61.
- De Giorgi V, Massi D, Carli P. Dermoscopy in the management of pigmented lesions of the oral mucosa. *Oral Oncol* 2003; 39(5):534-535.

IV. AMALGAM TATTOO

1. Harrison JD, Rowley PSA, Peters PD. Amalgam tattoos: light and electron microscopy and electron-probe microanalysis. *J Pathol* 1977; 121:83-92.
2. Owens BM, Johnson WW, Schuman NJ. Oral amalgam pigmentations (tattoos): a retrospective study. *Quintessence Int* 1992; 23:805-810.
3. Buchner A, Hansen LS. Amalgam pigmentation (amalgam tattoo) of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 1980; 49(2):139-147.
4. McHugh WD. Statement: effects and side effects of dental restorative materials. *Adv Dent Res* 1992; 6:139-144.
5. Kissel SO, Hanratty JJ. Periodontal treatment of an amalgam tattoo. *Compendium* 2002; 23(10):930-936.
6. McGinnis JP Jr., Greer JL, Daniels DS. Amalgam tattoo: report of an unusual clinical presentation and the use of energy dispersive X-ray analysis as an aid to diagnosis. *JADA* 1985; 110:52-54.
7. Hartman LC, Natiella JR, Mennaghan MA. The use of elemental microanalysis in verification of the composition of presumptive amalgam tattoo. *J Oral Maxillofac Surg* 1986; 44:628-633.

V. BENIGN MIGRATORY GLOSSITIS

1. Marks R, Radden BG. Geographic tongue: a clinico-pathological review. *Australas J Dermatol* 1981; 22:75-79.
2. Assimakopoulos D, Patrikakos G, Fotika C, et al. Benign migratory glossitis or geographic tongue: an enigmatic oral lesion. *Am J Med* 2002; 113:751-755.
3. Yarom N, Cantony U, Gorsky M. Prevalence of fissured tongue, geographic tongue and median rhomboid glossitis among Israeli adults of different ethnic origins. *Dermatology* 2004; 209(2):88-94.
4. Richardson ER. Incidence of geographic tongue and median rhomboid glossitis in 3,319 Negro college students. *Oral Surg Oral Med Oral Pathol* 1968; 26(5):623-625.
5. Aboyans V, Ghaemmaghami A. The incidence of fissured tongue among 4,009 Iranian dental outpatients. *Oral Surg Oral Med Oral Pathol* 1973; 36(1):34-38.
6. Meskin LH, Redman RS, Gorlin RJ. Incidence of geographic tongue among 3,668 students at the University of Minnesota. *J Dent Res* 1941; 116:16-21.
7. Chosack A, Zadik D, Eidelman E. The prevalence of scrotal tongue and geographic tongue in 70,359 Israeli schoolchildren. *Community Dent Oral Epidemiol* 1974; 2:253-257.
8. Shulman JD, Geach MM, Rivera-Hidalgo F. The prevalence of oral mucosal lesions in U.S. adults. *JADA* 2004; 135:1279-1286.
9. Shulman JD. Prevalence of oral mucosal lesions in children and youth in the USA. *Int J Paediatr Dent* 2005; 5(2):89-97.
10. Fenerli A, Papanicolaou S, Papanicolaou M, et al. Histocompatibility antigens and geographic tongue. *Oral Surg Oral Med Oral Pathol* 1993; 76:476-479.
11. Gonzaga HFS, Torres EA, Alchorne MMA, et al. Both psoriasis and benign migratory glossitis are associated with HLA-Cw6. *Br J Dermatol* 1996; 135:368-370.
12. Younai FS, Phelan JA. Oral mucositis with features of psoriasis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84:61-67.
13. Marks R, Scarff CE, Yap LM, et al. Fungiform papillary glossitis: atopic disease in the mouth? *Br J Dermatol* 2005; 153:740-745.
14. Jainkittivong A, Langlais RP. Geographic tongue: clinical characteristics of 188 cases. *J Contemp Dent Pract* 2005; 1(6):123-135.
15. Drezner DA, Schaffer SR. Geographic tongue. *Otolaryngol Head Neck Surg* 1997; 117(3 pt 1):291.
16. Pass B, Brown R, Childers E. Geographic tongue: literature review and case report. *Dent Today* 2005; 24(8):54; 56-57.

VI. MEDIAN RHOMBOID GLOSSITIS

1. Carter LC. Median rhomboid glossitis: review of a puzzling entity. *Compendium* 1990; 11(7):446, 448-51.
2. Espinoza I, Rojas R, Aranda W, et al. Prevalence of oral mucosal lesions in elderly people in Santiago, Chile. *J Oral Pathol Med* 2003; 32:571-575.
3. Cooke BE. Median rhomboid glossitis. *Br J Dermatol* 1975; 93(4):399-405.
4. Wright BA, Fenwick F. Candidiasis and atrophic tongue lesions. *Oral Surg Oral Med Oral Pathol* 1981; 51(1):55-61.
5. Allen CM, Blozis GG, Rosen S, et al. Chronic candidiasis of the rat tongue: a possible model for human median rhomboid glossitis. *J Dent Res* 1982; 61(11):1287-1291.
6. Deshpande RB, Bharucha MA. Median rhomboid glossitis: secondary to colonization of the tongue by actinomyces (a case report). *J Postgrad Med* 1991; 37:238-240.
7. Walsh LJ, Cleveland DB, Cumming CG. Quantitative evaluation of Langerhans cells in median rhomboid glossitis. *J Oral Pathol Med* 1992; 21:28-32.
8. Arendorf TM, Walker DM. Tobacco smoking and denture wearing as local aetiological factors in median rhomboid glossitis. *Int J Oral Surg* 1984; 13:411-415.
9. Barasch A, Saffort MM, Catalanotto FA, et al. Oral soft tissue manifestations in HIV-positive vs. HIV-negative children from an inner city population: a two-year observational study. *Pediatr Dent* 2000; 22(3):215-220.
10. Flaitz CM, Nichols CM, Hicks MJ. An overview of the oral manifestations of AIDS-related Kaposi's sarcoma. *Compend Contin Educ Dent* 1995; 16(2):136-138, 140, 142 passim (quiz 148).
11. Guggenheimer J, Moore PA, Rossie K, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. I. Prevalence and characteristics of non-candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 89:563-569.
12. Guggenheimer J, Moore PA, Rossie K, et al. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. II. Prevalence and characteristics of candida and non-candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 89:563-569.
13. Yamaoka Y, Suzuki A, Hatakeyama S, et al. Median rhomboid glossitis associated with amyloid deposition. *Acta Pathol Jpn* 1978; 28(2):319-323.
14. Zegarelli DJ. Fungal infections of the oral cavity. *Otolaryngol Clin North Am* 1993; 26(6):1069-1089.
15. Touyz LZG, Peters E. Candidal infection of the tongue with nonspecific inflammation of the palate. *Oral Surg Oral Med Oral Pathol* 1987; 63:304-308.
16. Wright BA. Median rhomboid glossitis: not a misnomer. *Oral Surg Oral Med Oral Pathol* 1978; 46(6):806-814.
17. Barrett AW, Kingsmill VJ, Speight PM. The frequency of fungal infection in biopsies of oral mucosal lesions. *Oral Dis* 1998; 4(1):26-31.
18. Terai H, Shimahara M. Atrophic tongue associated with candida. *J Oral Pathol Med* 2005; 14:397-400.
19. Holmstrup P, Axell T. Classification and clinical manifestations of oral yeast infections. *Acta Odontol Scand* 1990; 48:57-59.
20. Gorsky M, Raviv M, Taicher S. Squamous cell carcinoma mimicking median rhomboid glossitis region: report of a case. *J Oral Maxillofac Surg* 1993; 51:798-800.

VII. NICTOTINIC STOMATITIS

- Boysen F. Stomatitis nicotina. *Acta Otolaryngol Suppl* 1950; 95:20–23.
- Forsey RR, Sullivan TJ. Stomatitis nicotina. *Arch Dermatol* 1961; 83:945–950.
- Schwartz DL. Stomatitis nicotina of the palate. Report of two cases. *Oral Surg Oral Med Oral Pathol* 1965; 20(3): 306–315.
- Fisher AA. Contact stomatitis. *Dermatol Clin* 1987; 5(4): 709–717.
- Mirbod SM, Ahing SI. Tobacco-associated lesions of the oral cavity: Part I. nonmalignant lesions. *J Can Dent Assoc* 2000; 66:252–256.
- Taybos G. Oral changes associated with tobacco use. *Am J Med Sci* 2003; 326(4):179–182.
- Reddy CRRM, Rajakumari K, Ramulu C. Regression of stomatitis nicotina in persons with a long standing habit of reverse smoking. *Oral Surg Oral Med Oral Pathol* 1974; 38(4):570–583.
- Van Wyk CW. Nicotinic stomatitis of the palate: a clinico-histological study. *J Dent Assoc S Afr* 1967; 15:22(4):106–111.
- Reddy CRRM, Kameswari VR, Ramulu C, et al. Histopathological study of stomatitis nicotina. *Br J Cancer* 1971; 25(3):403–410.

VIII. HAIRY TONGUE

- Sarti GM, Haddy RI, Schaffer D, et al. Black hairy tongue. *Am Fam Physician* 1990; 41(6):1751–1755.
- Regezi JA, Scuibba JJ, eds. *Oral Pathology Clinical-Pathologic Correlations*. 2nd ed. Philadelphia, PA: WB Saunders, 1989:183–184.
- Waggoner WC, Volpe AR. Lingua villosa nigra – a review of black hairy tongue. *J Oral Med* 1967; 22(1):18–21.
- Darwazeh AMG, Pillai K. Prevalence of tongue lesions in 1013 Jordanian dental outpatients. *Community Dent Oral Epidemiol* 1993; 21:323–324.
- Redman RS. Prevalence of geographic tongue, fissured tongue, median rhomboid glossitis, and hairy tongue among 3,611 Minnesota schoolchildren. *Oral Surg Oral Med Oral Pathol* 1970; 30(3):390–395.
- Abbey L, Shklar G. Hairy tongue with bilateral peripheral lesions. *J Oral Med* 1971; 26(1):32–34.
- Farman AG. Hairy tongue (lingua villosa). *J Oral Med* 1977; 32(3):85–91.
- Avcu N, Ozbek M, Kurtoglu D, et al. Oral findings and health status among hospitalized patients with physical disabilities, aged 60 or above. *Arch Gerontol Geriatr* 2005; 41(1):69–79.
- Cheshire WP Jr. Unilateral black hairy tongue in trigeminal neuralgia. *Headache* 2004; 44:908–910.
- Levine N. Dark discoloration of the tongue. *Geriatrics* 1996; 51(6):20.
- Christen AG, Swanson BZ Jr. Oral hygiene: a history of tongue scraping and brushing. *JADA* 1978; 96:215–219.
- Bhaskar SN. Oral lesions in the aged population. *Geriatrics* 1968; 23(10):137–149.
- Bartels HA, Maillard ER. Studies in diagnosis in oral surgery and oral medicine. 1955; 8(6):659–663.
- Ramadan AE. The association of black hairy tongue with toothpastes containing neomycin. Report of two cases. *Egypt Dent J* 1969; 15(4):253–256.
- Heymann WR. Psychotropic agent-induced black hairy tongue. *Cutis* 2000; 66(1):25–26.
- Paganini AE, Zlotlow M. Hairy tongue in patients receiving phenothiazines: preliminary report. *Am J Psychiatry* 1959; 116:362–363.

- Anderson G, Vala EK. The influence of cigarette consumption and smoking machine yields of tar and nicotine on the nicotine uptake and oral mucosal lesions in smokers. *J Oral Pathol Med* 1997; 26:117–123.
- Meltzer L, Farfel B. Unilateral hairy tongue. *AMA Arch Derm Syphilol* 1954; 69(4):497–498.
- Winzer M, Gilliar U, Ackerman AB. Hairy lesions of the oral cavity. *Am J Dermatopathol* 1988 10(2):155–159.
- Manabe M, Lim HW, Winzer M, et al. Architectural organization of filiform papillae in normal and black hairy tongue epithelium. *Arch Dermatol* 1999; 135:177–181.
- Svejda J, Skach M, Plaackova A. Hairlike variations of filiform papillae in the human tongue. *Oral Surg Oral Med Oral Pathol* 1977; 43(1): 97–105.
- Harda Y. Black hairy tongue. A scanning electron microscopic study. *J Laryngol Otol* 1977; 91(1):91–96.
- Langtry JA, Carr MM, Steele MC, et al. Topical tretinoin: a new treatment for black hairy tongue (lingua villosa nigra). *Clin Exp Dermatol* 1992; 17(3):163–164.
- Standish M, Moorman WC. Treatment of hairy tongue with podophyllin resin. *J Am Dent Assoc* 1964; 68:535–540.
- Hasler JF, Standish SS. Podophyllin treatment of hairy tongue: a warning. *J Am Dent Assoc* 1969; 78(3):563–567.
- McGregor JM, Hay RJ. Oral retinoids to treat black hairy tongue. *Clin Exp Dermatol* 1993; 18(3):291.

IX. ORAL HAIRY LEUKOPLAKIA

- Greenspan D, Greenspan JS. Significance of oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol* 1992; 73: 151–154.
- Boulter AW, Soltanpoor N, Swan AV, et al. Risk factors associated with Epstein-Barr virus replication in oral epithelial cells of HIV-infected individuals. *AIDS* 1996; 10:935–940.
- Patton LL, Phelan JA, Ramos-Gomez FJ, et al. Prevalence and classification of HIV-associated oral lesions. *Oral Dis* 2002; 8:98–109.
- Coogan MM, Greenspan J, Challacombe SJ. Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ* 2005; 83(9):700–706.
- Patel ASH, Glick M. Oral manifestations associated with HIV infection: evaluation, assessment and significance. *Gen Dent* 2003; 51(2):153–156.
- Arendorf TM, Bredekamp B, Cloete CAC, et al. Oral manifestations of HIV infection in 600 South African patients. *J Oral Pathol Med* 1998; 27:176–179.
- Frezzi C, Leao JC, Porter S. Current trends of HIV disease of the mouth. *J Oral Pathol Med* 2005; 24:513–531.
- Bruce AJ, Rogers RS III. Oral manifestations of sexually transmitted diseases. *Clin Dermatol* 2004; 22(6):520–527.
- De Faria PR, Vargas PA, Saldiva PHN, et al. Tongue disease in advanced AIDS. *Oral Dis* 2005; 11:72–80.
- Green TL, Greenspan JS, Greenspan D, et al. Oral lesions mimicking hairy leukoplakia: a diagnostic dilemma. *Oral Surg Oral Med Oral Pathol* 1989; 67:422–426.
- Okunseri C, Badner V, Wiznia A, et al. Prevalence of oral lesions and percent CD4⁺ t-lymphocytes in HIV-infected children on antiretroviral therapy. *AIDS Patient Care STDS* 2003; 17(1):5–11.
- Greenspan D, Gange SJ, Phelan JA, et al. Incidence of oral lesions in HIV-1-infected women: reduction with HAART. *J Dent Res* 2004; 83(2):145–150.
- Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, et al. The changing clinical spectrum of human immunodeficiency virus. *Medicine (Baltimore)* 2003; 82(1):39–50.
- Marcus M, Maida CA, Freed JR, et al. Oral white patches in a national sample of medical HIV patients in the era of HAART. *Community Dent Oral Epidemiol* 2005; 33:99–106.

15. Walling DM, Ling PD, Gordadze AV, et al. Expression of Epstein-Barr virus latent genes in oral epithelium: determinants of the pathogenesis of oral hairy leukoplakia. *JID* 2004; 190:396–399.
16. Lilly EA, Cameron JE, Shetty KV, et al. Lack of evidence for local immune activity in oral hairy leukoplakia and oral wart lesions. *Oral Microbiol Immunol* 2005; 20:154–162.
17. Rigopoulos D, Pappas V, Katsambas A. Cutaneous markers of HIV infection. *Clin Dermatol* 2004; 22(6):487–498.
18. Hermann K, Frangou P, Middeldorp J, et al. Epstein-Barr virus replication in tongue epithelial cells. *J Gen Virol* 2002; 83(pt 12):2995–2998.
19. Walling DM, Flaitz CM, Nichols CM, et al. Persistent productive Epstein-Barr virus replication of normal epithelial cells in vivo. *J Infect Dis* 2001; 184(12):1499–1507.
20. Walling DM, Etienne W, Ray AJ, et al. Persistence and transition of Epstein-Barr virus genotypes in the pathogenesis of oral hairy leukoplakia. *J Infect Dis* 2004; 190:387–395.
21. Brandwein M, Nuovo G, Ramer M, et al. Epstein-Barr virus reactivation in hairy leukoplakia. *Mod Pathol* 1996; 9(3):298–303.
22. Walling DM, Flaitz CM, Hosein FG, et al. Effect of Epstein-Barr virus replication on Langerhans cells in pathogenesis of oral hairy leukoplakia. *J Infect Dis* 2004; 189:1656–1663.
23. Ficarra G, Gaglioti D, Di Pietro M, et al. Oral hairy leukoplakia: clinical aspects, histologic morphology and differential diagnosis. *Head Neck* 1991; 13:524–521.
24. Aquilina C, Viraben R, Denis P. Secondary syphilis simulating oral hairy leukoplakia. *J Am Acad Dermatol* 2003; 49(4):749–751.
25. McCreary CE, Flint SR, McCartan BE, et al. Uremic stomatitis mimicking oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 83:350–353.
26. Fluckiger R, Laifer G, Itin P, et al. Oral hairy leukoplakia in a patient with ulcerative colitis. *Gastroenterology* 1994; 106(2):506–508.
27. Casiglia J, Woo S. Oral hairy leukoplakia as an early indicator of Epstein-Barr virus-associated post-transplant lymphoproliferative disorder. *J Oral Maxillofac Surg* 2002; 60:948–950.
28. Blomgren J, Back H. Oral hairy leukoplakia in a patient with multiple myeloma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 82:408–410.
29. Nicolatou O, Nikolatos G, Fisis M, et al. Oral hairy leukoplakia in a patient with acute lymphocytic leukemia. *Oral Dis* 1999; 5:76–79.
30. Epstein JB, Sherlock CH, Wolber RA. Hairy leukoplakia after bone marrow transplantation. *Oral Surg Oral Med Oral Pathol* 1993; 75:690–695.
31. Laine PO, Lindqvist JC, Pyrhonen SO, et al. Lesions of the oral mucosa in lymphoma patients receiving cytostatic drugs. *Eur J Cancer B Oral Oncol* 1993; 29B(4):291–294.
32. De Kaminsky AR, Kaminsky C, Blanco GF, et al. Hairy leukoplakia in an HIV-seronegative patient. *Int J Dermatol* 1995; 34(6):420–424.
33. Itin PH, Cajacob A, Langauer S, et al. Pseudo hairy leukoplakia. *Br J Dermatol* 1993; 128(5):589–591.
34. Southam JC, Felix DH, Wray D, et al. Hairy leukoplakia – a histological study. *Histopathology* 1991; 19(1):63–67.
35. Fernandez JF, Benito MAC, Lizalde EB, et al. Oral hairy leukoplakia: a histopathologic study of 32 cases. *Am J Dermatopathol* 1990; 12(6):571–578.
36. Migliorati CA, Jones AC, Baughman PA. Use of exfoliative cytology in the diagnosis of oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol* 1993; 76:704–710.
37. Dias EP, Rocha ML, Silva A, et al. Histopathologic and cytopathologic features of a subclinical phase. *Am J Clin Pathol* 2000; 114:395–401.
38. Gulley ML. Molecular diagnosis of Epstein-Barr virus-related diseases. *J Mol Diagn* 2001; 3(1):1–10.
39. Hamilton-Dutoit SJ, Pallesen G. Detection of Epstein-Barr virus small RNAs in routine paraffin sections using non-isotopic RNA/RNA in situ hybridization. *Histopathology* 1994; 25:101–111.
40. Mabruk MJEMF, Antonio M, Flint SR, et al. A simple and rapid technique for the detection of Epstein-Barr virus DNA in HIV-associated oral hairy leukoplakia biopsies. *J Oral Pathol Med* 2000; 29:118–122.
41. Guccion JG, Redman RS. Oral hairy leukoplakia: an ultrastructural study and review of the literature. *Ultrastruct Pathol* 1999; 23(3):181–187.
42. Greenspan JS, Rabanus JP, Petersen V, et al. Fine structure of EBV-infected keratinocytes in oral hairy leukoplakia. *J Oral Pathol Med* 1989; 18:565–572.
43. Epstein JB, Fatahzadeh M, Matisic J, et al. Exfoliative cytology and electron microscopy in the diagnosis of hairy leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 79:564–569.
44. Manca V, Mongiardo N, Pellegrino F, et al. Oral hairy leukoplakia in AIDS patients: an ultrastructural study. *J Dermatol* 1990; 17(12):729–736.

X. FOCAL EPITHELIAL HYPERPLASIA (HECK'S DISEASE)

1. Neville BW, Damm DD, Allen CM, et al., eds. *Oral & Maxillofacial Pathology*. Philadelphia, PA: WB Saunders, 2001:265–266.
2. Shafer WG, ed. *A Textbook of Oral Pathology* Philadelphia: WB Saunders, 1983:22–23.
3. Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: An unusual oral mucosal lesion found in Indian children. *Oral Surg Oral Med Oral Pathol* 1965; 20:201–212.
4. Pretorius-Clausen F, Willis JM. Papova virus-like particles in focal epithelial hyperplasia. *Scand J Dent Res* 1971; 79: 362–365.
5. Carlos R, Sedano HO. Multifocal papilloma virus epithelial hyperplasia. *Oral Surg Oral Med Oral Pathol* 1994; 77: 631–635.
6. Estrada L. Informe preliminar sobre algunos aspectos odontologicos de los indios caramanta. *Boletin del instituto de Antropologia* 1956; 1:319–321.
7. Pretorius-Clausen F. Geographical aspects of oral focal epithelial hyperplasia. *Pathol Microbiol* 1973; 39:204–213.
8. Vilmer C, Cavelier-Balloy B, Pinquier L, et al. Focal epithelial hyperplasia and multifocal human papillomavirus infection in an HIV-seropositive man. *J Am Acad Dermatol* 1994; 30(3):497–498.
9. Pfister H, Hettich I, Runne U, et al. Characterization of human papillomavirus type 13 from focal epithelial hyperplasia Heck lesions. *J Virol* 1983; 47(2):363–366.

XI. CONDYLOMA ACUMINATUM

1. Choukas NC, Toto PD. Condylomata acuminatum of the oral cavity. *Oral Surg Oral Med Oral Pathol* 1982; 54(4): 480–485.
2. Jenson AB, Lancaster WD, Hartmann DP, et al. Frequency and distribution of papillomavirus structural antigens in verrucae, multiple papillomas, and condylomata of the oral cavity. *Am J Pathol* 1982; 107:212–218.
3. Shaffer EL Jr., Reiman BEF, Gysland WB. Oral condyloma acuminatum. *J Oral Pathol* 1980; 9:163–173.
4. Butler S, Molinari JA, Plezia RA, et al. Condyloma acuminatum in the oral cavity: four cases and a review. *Rev Infect Dis* 1988; 10(3):544–550.

5. Knapp MJ, Uohara GI. Oral condyloma acuminatum. *Oral Surg Oral Med Oral Pathol* 1967; 23(4):538-545.
6. Flaitz CM. Condyloma acuminatum of the floor of the mouth. *Am J Dent* 2001; 14:155-116.
7. Anderson KM, Perez-Montiel D, Miles L, et al. The histologic differentiation of oral condyloma acuminatum from its mimics. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96:420-428.
8. Leigh J. Oral warts rise dramatically with use of new agents in HIV. *HIV Clin* 2000; 12(2):7.
9. Greenspan D, Canchola AJ, MacPhail LA, et al. Effect of highly active antiretroviral therapy on frequency of oral warts. *Lancet* 2001; 357:1411-1412.
10. Greenspan D, Gange SJ, Phelan JA, et al. Incidence of oral lesions in HIV-1 infected women: reduction with HAART. *J Dent Res* 2004; 83(2):145-150.
11. Esmeili T, Lozada-Nur F, Epstein J. Common benign oral soft tissue masses. *Dent Clin N Am* 2005; 49:223-240.
12. Correll RW, Carroll GW. Multiple, painless, verruciform nodules on the mucosa of the lower lip. *JADA* 1986; 112:97-98.
13. Regezi JA, Greenspan D, Greenspan JS. HPV-associated epithelial atypia in oral warts in HIV⁺ patients. *J Cutan Pathol* 1994; 21:217-223.
14. Zunt SL, Tomich CE. Oral condyloma acuminatum. *J Dermatol Surg Oncol* 1989; 15:591-594.
15. Eversole LR, Laipis PJ, Merrell P, et al. Demonstration of human papillomavirus DNA in oral condyloma acuminatum. *J Oral Pathol* 1987; 16:266-272.

XII. VERRUCA VULGARIS

1. Praetorius F. HPV-associated diseases of oral mucosa. *Clin Dermatol* 1997; 15(3):399-413.
2. Adler-Storthz K, Newland JR, Tessin BA, et al. Identification of human papillomavirus types in oral verrucae vulgaris. *J Oral Pathol* 1986; 15:230-233.
3. Bhatia B, Jain VK, Bhatia KK, et al. Verruca - vulgaris of oral cavity. *J Indian Dent Assoc* 1987; 59(6-9):147-149.
4. Premoli de Percoco G, Galindo I, Ramirez JL, et al. Detection of human papillomavirus-related oral verruca vulgaris among Venezuelans. *J Oral Pathol Med* 1993; 22(3):113-116.
5. Green TL, Eversole LR, Leider AS. Oral and labial verrucae vulgaris: clinical, histologic and immunohistochemical evaluation. *Oral Surg Oral Med Oral Pathol* 1986; 62(4):410-416.
6. Eversole LR, Laipis PJ, Green TL. Human papillomavirus type 2 DNA in oral and labial verrucae vulgaris. *J Cutan Pathol* 1987; 14:319-325.
7. Terezhalmay GT, Riley CK, Moore WS, et al. Oral verrucae vulgaris. *Quintessence Int* 2002; 33(2):162-163.
8. Danforth RA, Green TL. Oral warty dyskeratoma. *Oral Surg Oral Med Oral Pathol* 1980; 49(6):523-525.
9. Harrist TJ, Murphy GF, Mihm MC Jr. Oral warty dyskeratoma. *Arch Dermatol* 1980; 116:929-931.
10. Palefsky JM, Silverman JR S, Abdel-Salaam M, et al. Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. *J Oral Pathol Med* 1995; 24:193-197.

XIII. PAPILLOMA

1. Syrjanen S. Human papillomavirus infections and oral tumors. *Med Microbiol Immunol* 2003; 192:123-138.
2. Bouquot JE, Wroblewski GJ. Papillary (pebbled) masses of the oral mucosa: more than simple papillomas. *Pract Periodontics Aesthet Dent* 1996; 8(6):533-543 (quiz 543).

3. Abbey LM, Page DG, Sawyer DR. The clinical and histopathologic features of a series of 464 oral squamous cell papillomas. *Oral Surg Oral Med Oral Pathol* 1980; 49(5):419-428.
4. Tay ABG. A 5-year survey of oral biopsies in an oral surgical unit in Singapore: 1993-1997. *Ann Acad Med Singapore* 1999; 28:665-671.
5. Greer RO, Goldman HM. Oral papillomas. Clinicopathologic evaluation and retrospective examination for dyskeratosis in 110 lesions. *Oral Surg Oral Med Oral Pathol* 1974; 38(3):435-440.
6. Yamaguchi T, Shindoh M, Amemiya A, et al. Detection of human papillomavirus type 2 related sequence in oral papilloma. *Anal Cell Pathol* 1998; 16(3):125-130.
7. Eversole LR, Laipis PJ. Oral squamous papillomas: detection of HPV DNA by in situ hybridization. *Oral Surg Oral Med Oral Pathol* 1988; 65:545-550.
8. Loning TH, Reichart P, Staquet MJ, et al. Occurrence of papillomavirus structural antigens in oral papillomas and leukoplakias. *J Oral Pathol* 1984; 13(2):155-165.
9. Padayachee A, Van Wyk CW. Human papillomavirus (HPV) in oral squamous cell papillomas. *J Oral Pathol* 1987; 16:353-355.
10. Copete MA, Wendt K, Chen S-Y. Expression of p53, Ki-67 and Cytokeratin-4 (CK4) in oral papillomas. *J Oral Pathol Med* 1997; 26:211-216.
11. Ward KA, Napier SS, Winter PC, et al. Detection of human papilloma virus DNA sequences in oral squamous cell papillomas by the polymerase chain reaction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 80:63-66.
12. Syrjanen S, Puranen M. Human papillomavirus infections in children: the potential role of maternal transmission. *Crit Rev Oral Biol Med* 2000; 11(2):259-274.
13. Puranen M, Yliskoski M, Saarkoski S, et al. Vertical transmission of human papillomavirus from infected mothers to their newborn babies and persistence of the virus in childhood. *Am J Obstet Gynecol* 1996; 174:694-699.
14. Terai M, Hashimoto K, Yoda K, et al. High prevalence of human papillomaviruses in the normal oral cavity of adults. *Oral Microbiol Immunol* 1999; 14:201-205.
15. Eversole LR. Papillary lesions of the oral cavity: relationship to human papillomaviruses. *J Calif Dent Assoc* 2000; 28(12):922-927.

XIV. VERRUCIFORM XANTHOMA

1. Shafer WG. Verruciform xanthoma. *Oral Surg Oral Med Oral Pathol* 1971; 31:784-789.
2. Neville B. The verruciform xanthoma. A review and report of eight new cases. *Am J Dermatopathol* 1986; 8(3): 247-253.
3. Toida M, Koizumi H. Verruciform xanthoma involving the lip: a case report. *J Oral Maxillofac Surg* 1993; 51:432-434.
4. Oliveira PT, Jaeger RG, Cabral LAG, et al. Verruciform xanthoma of the oral mucosa. Report of four cases and a review of the literature. *Oral Oncol* 2001; 37(3):326-331.
5. Agarwal-Antal N, Zimmermann J, Scholz T, et al. A giant verruciform xanthoma. *J Cutan Pathol* 2002; 29:119-124.
6. Drummond JF, White DK, Dam DD, et al. Verruciform xanthoma within carcinoma in situ. *J Oral Maxillofac Surg* 1989; 47(4):398-400.
7. Miyamoto Y, Nagayama M, Hayasi Y. Verruciform xanthoma occurring within oral lichen planus. *J Oral Pathol Med* 1996; 25:188-191.
8. Pouloupoulos AK, Epivatianos A, Zaraboukas T, et al. Verruciform xanthoma coexisting with oral discoid lupus erythematosus. *Br J Oral Maxillofac Surg* 2001; 37(3):326-331.

9. Polonowita AD, Firth NA, Rich AM. Verruciform xanthoma and concomitant lichen planus of the oral mucosa. *Int J Oral Maxillofac* 1999; 28:62–66.
10. Iamaroon A, Vickers RA. Characterization of verruciform xanthoma by in situ hybridization and immunohistochemistry. *J Oral Pathol Med* 1996; 25:395–400.
11. Hu J, Li Y, Li S. Verruciform xanthoma of the oral cavity: clinicopathological study relating to pathogenesis. Report of three cases. *APMIS* 2005; 113(9):629–634.
12. Damm DD, Fantasia JE. Red, bumpy palate. Inflammatory papillary hyperplasia. *Gen Dent* 2002; 50(4):378, 380.
13. Cobb CM, Holt R, Denys FR. Ultrastructural features of the verruciform xanthoma. *J Oral Pathol* 1976; 5(1):42–51.
14. Philipsen HP, Reichart PA, Takata T, et al. Verruciform xanthoma-biological profile of 282 oral lesions based on a literature survey with nine new cases from Japan. *Oral Oncol* 2003; 39(4):325–336.
15. Van der Waal I, Kerstins HCJ, Hens CJJ. Verruciform xanthoma of the oral mucosa. *J Oral Maxillofac Surg* 1985; 43(8):623–626.
16. Mostafa KA, Takata T, Ogawa I, et al. Verruciform xanthoma of the oral mucosa: a clinicopathological study with immunohistochemical findings relating to pathogenesis. *Virchows Arch A Pathol Anat Histopathol* 1993; 423(4):243–248.
17. Shin HI, Choy KS, Nagasaki H, et al. Verruciform xanthoma of the oral mucosa: an immunohistochemical and ultrastructural study of two cases. *Oral Oncol* 1997; 33(4):279–283.
18. Orchard GE, Jones EW, Jones RR. Verruciform xanthoma: an immunocytochemical study. *Br J Biomed Sci* 1994; 51(1):28–34.

XV. DRUG-INDUCED GINGIVAL HYPERPLASIA

1. Guggenheimer J. Oral manifestations of drug therapy. *Dent Clin North Am* 2002; 46:857–868.
2. Abdollahi M, Radfar M. A review of drug-induced oral reactions. *J Contemp Dent Pract* 2003; 1(4):10–31.
3. Kuru L, Yilmaz S, Kuru B, et al. Expression of growth factors in the gingival crevice fluid of patients with phenytoin-induced gingival enlargement. *Arch Oral Biol* 2004; 49:945–950.
4. Majola MP, McFadyen ML, Connolly C, et al. Factors influencing phenytoin-induced gingival enlargement. *J Clin Periodontol* 2000; 27:506–512.
5. Das SJ, Newman HN, Olsen I. Keratinocyte growth factor receptor is up-regulated in cyclosporine A-induced gingival hyperplasia. *J Dent Res* 2002; 81(10):683–687.
6. Yamada H, Nishimura F, Naruishi K, et al. Phenytoin and cyclosporine A suppress the expression of MMP-1, TIMP-1, and cathepsin L, but not cathepsin B in cultured gingival fibroblasts. *J Periodontol* 2000; 71(6):955–960.
7. Sinha S, Kamath V, Arunodaya GR, et al. Phenobarbitone induced gingival hyperplasia. *J Neurol Neurosurg Psychiatry* 2002; 73:597–603.
8. Tokgoz B, San HI, Yildiz O. Effects of azithromycin on cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc* 2004; 36(9):2699–2702.
9. Jaiarj N. Drug-induced gingival overgrowth. *J Mass Dent Soc* 2003; 52(3):16–20.
10. Yoshida T, Nagata J, Yamane A. Growth factors and proliferation of cultured rat gingival cells in response to cyclosporine A. *J Periodont Res* 2005; 40:11–19.
11. Shouda J, Nakamoto H, Sugahara S. Incidence of gingival hyperplasia caused by calcium antagonists in continuous ambulatory peritoneal dialysis patients. *Adv Perit Dial* 1999; 15:153–155.

12. Haniastuti T, Santoso AS, Agustiono P, et al. Effect of nifedipine on the expression of p53 protein in rat gingival. *Biomed Pharmacother* 2002; 56:235–240.
13. Shimizu Yasuki, Kataoka M, Seto H. Nifedipine induces gingival epithelial hyperplasia in rats through inhibition of apoptosis. *J Periodontol* 2002; 73:861–867.
14. Nery EB, Edson RG, Lee KK, et al. Prevalence of Nifedipine-induced gingival hyperplasia. *J Periodontol* 1995; 66:572–578.
15. Seymour RA, Thomason JM, Ellis JS. The pathogenesis of drug-induced gingival overgrowth. *J Clin Periodontol* 1996; 23:165–175.

XVI. DENTURE-INDUCED FIBROUS HYPERPLASIA

1. Buchner A, Helft M. Pathologic conditions of the oral mucosa associated with ill-fitting dentures: III. Epulis fissuratum and flabby ridge. *Refuat Hapeh Vehashinayim* 1979; 28:7–13.
2. Bouquot JE, Gundlach KKH. Oral exophytic lesions in 23,616 white Americans over 35 years of age. *Oral Surg Oral Med Oral Pathol* 1986; 62:284–291.
3. Cutright DE. The histopathologic findings in 583 cases of epulis fissuratum. *Oral Surg Oral Med Oral Pathol* 1974; 37:401–411.
4. Thomas GA. Denture-induced fibrous inflammatory hyperplasia (epulis fissuratum): research aspects. *Austral Prosthodont* 1993; 7:49–53.

XVII. INFLAMMATORY PAPILLARY HYPERPLASIA

1. Bhaskar SN, Beasley JD III, Cutright DE. Inflammatory papillary hyperplasia of the oral mucosa: report 341 cases. *JADA* 1970; 81:949–952.
2. Wescott WB, Correll RW. Multiple papillary projections on the alveolar mucosa and palate. *JADA* 1984; 108:91–92.
3. Salonen MA, Raustia AM, Oikarinen KS. Effect of treatment of palatal inflammatory papillary hyperplasia with local and system antifungal agents accompanied by renewal of complete dentures. *Acta Odontol Scand* 1996; 54:87–91.
4. Monaco JG, Pickett AB. The role of Candida in inflammatory papillary hyperplasia. *J Prosthet Dent* 1981; 45(5):470–471.
5. Thwaites MS, Jeter TE, Ajagbe O. Inflammatory papillary hyperplasia: review of literature and case report involving a 10-year-old child. *Quintessence Int* 1990; 21:133–138.
6. Cutright DE. Morphogenesis of inflammatory papillary hyperplasia. *J Prosthet Dent* 1975; 33(4):380–385.
7. Bergendal T, Heimdahl A, Isacson G. Surgery in the treatment of denture-related inflammatory papillary hyperplasia of the palate. *Int J Oral Surg* 1980; 9:312–319.

XVIII. IRRITATION FIBROMA

1. Esmeili T, Lozada-Nur F, Epstein J. Common benign oral soft tissue masses. *Dent Clin North Am* 2005; 49:223–240.
2. Barker DS, Lucas RB. Localised fibrous overgrowth of the oral mucosa. *Br J Oral Surg* 1967; 5:86–92.
3. Dayan D, Bodner L, Hammel I, et al. Histochemical characterization of collagen fibers in fibrous overgrowth (irritation fibroma) of the oral mucosa: effect of age and duration of lesions. *Arch Gerontol Geriatr* 1994; 18(1):53–57.
4. Bakos LH. The giant cell fibroma: a review of 116 cases. *Ann Dent* 1992; 51(1):32–35.

5. Savage NW, Monsour PA. Oral fibrous hyperplasias and the giant cell fibroma. *Aust Dent J* 1985; 30(6):405-409.

XIX. GIANT CELL FIBROMA

1. Weathers DR, Callihan MD. Giant-cell fibroma. *Oral Surg* 1974; 37:374-384.
2. Houston GD. The giant cell fibroma. a review of 464 cases. *Oral Surg Oral Med Oral Pathol* 1982; 53(6):582-587.
3. Savage NW, Monsour PA. Oral fibrous hyperplasias and the giant cell fibroma. *Aust Dent J* 1985; 30(6):405-409.
4. Bakos LH. The giant cell fibroma: a review of 116 cases. *Ann Dent* 1992; 51(1):32-35.
5. Swan RH. Giant cell fibroma. A case presentation and review. *J Periodontol* 1988; 59(5):338-340.
6. Weathers DR, Campbell WG. Ultrastructure of the giant-cell fibroma of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 1974; 8(4):550-561.
7. Magnusson BC, Rasmusson LG. The giant cell fibroma. *Acta Odontol Scand* 1995; 53:293-296.
8. Souza LB, Andrade ESS, Miguel MCC, et al. Origin of stellate giant cells in oral fibrous lesions determined by immunohistochemical expression of vimentin, HHF-35, CD68 and factor XIIIa. *Pathology* 2004; 36(4):316-320.
9. Waldron CA. Giant-cell fibroma. *Oral Surg Oral Med Oral Pathol* 1974; 37(3):374-384.

XX. TONSILLITIS AND TONSILLAR HYPERPLASIA

1. Nave H, Gebert A, Pabst R. Morphology and immunology of the human palatine tonsil. *Anat Embryol* 2001; 204: 367-373.
2. Heffner DK. Pathology of the tonsils and adenoids. *Otolaryngol Clin North Am* 1987; 20:279-286.
3. Paulussen C, Claes J, Claes G, et al. Adenoids and tonsils, indications for surgery and immunological consequences of surgery. *Acta Oto-Rhino-Laryngo Belg* 2000; 54:403-408.
4. Go M, Kojima T, Ken-ichi T, et al. Expression and function of tight junctions in the crypt epithelium of human palatine tonsils. *J Histo Cyto* 2004; 52:1627-1638.
5. Chen HL, Chiou SS, Hsiao HP, et al. Respiratory adenoviral infections in children: a study of hospitalized cases in southern Taiwan in 2001-2002. *J Trop Pediatr* 2004; 50(5): 279-284.
6. Yamanaka N, Kataura A. Viral infections associated with recurrent tonsillitis. *Acta Otolaryngol Suppl* 1984; 416:30-37.
7. Yoda K, Sata T, Kurata T, et al. Oropharyngotonsillitis associated with nonprimary Epstein-Barr virus infection. *Arch Otolaryngol Head Neck Surg* 2000; 126:185-193.
8. Brodsky L, Moore L, Ogra PL, et al. The immunology of tonsils in children: the effect of bacterial load on the presence of B- and T-cell subsets. *Laryngoscope* 1988; 98:93-98.
9. Post JC, Stoodley P, Hall-Stoodley L, et al. The role of biofilms in otolaryngologic infections. *Curr Opin Otolaryngol Head Neck Surg* 2004; 12:185-190.
10. Chole RA, Faddis BT. Anatomical evidence of microbial biofilms in tonsillar tissues. *Arch Otolaryngol Head Neck Surg* 2003; 129:634-636.
11. Brodsky L, Frankel S, Gorfien J, et al. The role of dendritic cells in the development of chronic tonsillar disease in children. *Acta Otolaryngol Suppl* 1996; 523:98-100.
12. Richardson MA. Sore throat, tonsillitis and adenoiditis. *Med Clin North Am* 1999; 83(1):75-83.
13. Tewfik TL, Garni MA. Tonsillopharyngitis: clinical highlights. *J Otolaryngol* 2005; 34(suppl1):S45-S49.
14. Bieluch VM, Chasin WD, Martin ET, et al. Recurrent tonsillitis: histologic and bacteriologic evaluation. *Ann Otol Rhinol Laryngol* 1989; 98:332-335.
15. Kuhn J, Brook I, Waters C, et al. Quantitative bacteriology of tonsil removed from children with tonsillitis, hypertrophy and recurrent tonsillitis with and without hypertrophy. *Acta Otol Rhinol Laryngol* 1995; 104:646-652.
16. Casselbrant ML. What is wrong in chronic adenoiditis/ tonsillitis anatomical considerations. *Int J Pediatr Otorhinolaryngol* 1999; 49(suppl 1):S133-S135.
17. Johnson BC, Alvi A. Cost-effective workup for tonsillitis. *Postgrad Med* 2003; 113:115-119.
18. Heubi C, Shott SR. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections- an uncommon, but important indication for tonsillectomy. *Int J Ped Otorhinolaryng* 2003; 67:837-840.
19. Altemani A, Endo LH, Chone C, et al. Histopathological concept of chronic tonsillitis in children. *Acta Otolaryngol Suppl* 1996; 523:14-16.
20. Zhang PC, Pang YT, Loh KS, et al. Comparison of histology between recurrent tonsillitis and tonsillar hypertrophy. *Clin Otolaryngol* 2003; 28:235-239.
21. Wenig BM, Thompson LDR, Frankel SS, et al. Lymphoid changes of the nasopharyngeal and palatine tonsils that are indicative of human immunodeficiency virus infection. *Am J Surg Pathol* 1996; 20:572-587.
22. Gnepp DR, Souther J. Skeletal muscle in routine tonsillectomy specimens: a common finding. *Hum Pathol* 2000; 31:813-816.
23. Akkawi NM, Borroni B, Magoni M, et al. Lemierre's syndrome complicated by carotid thrombosis. *Neurol Sci* 2001; 22:403-404.
24. Griffies WS, Wotowic P, Wildes TO. Spontaneous tonsillar hemorrhage. *Laryngoscope* 1988; 98:365-368.
25. Bisno AL, Gerber MA, Gwaltney JM Jr., et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 2002; 35(2): 113-125.
26. Edmondson MB, Farwell KR. Relationship between the clinical likelihood of group A streptococcal pharyngitis and the sensitivity of a rapid antigen-detection test in a pediatric practice. *Pediatrics* 2005; 115(2):280-285.
27. Rimoin AW, Hamza HS, Vince A, et al. Evaluation of the WHO clinical decision rule for streptococcal pharyngitis. *Arch Dis Child* 2005; 90:1066-1070.
28. Abdul-Baqi KJ, Shakhathreh FMN. Effectiveness of treatment of tonsillopharyngitis: comparative study. *J Laryngol Otol* 2002; 116(11):917-919.
29. Gerber MA. Rapid diagnosis of pharyngitis caused by Group A Streptococci. *Clin Microbiol Rev* 2004; 17:571-580.
30. Gerber MA. Diagnosis and treatment of pharyngitis in children. *Pediatr Clin North Am* 2005; (3):729-747.
31. Syrogiannopoulos GA, Bozdogan B, Grivea JN, et al. Two dosages of clarithromycin for five days, amoxicillin/ clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 2004; 23:857-865.
32. Curtin CD, Casey JR, Murray PC, et al. Efficacy of cephalexin two vs. three times daily vs. cefadroxil once daily for streptococcal tonsillopharyngitis. *Clin Pediatr (Phila)* 2003; 42(6):519-526.
33. Brook I. The role of bacterial interference in otitis, sinusitis and tonsillitis. *Otolaryngol Head Neck Surg* 2005; 133(1): 139-146.
34. Curtin JM. The history of tonsil and adenoid surgery. *Otolaryngol Clin North Am* 1987; 20(2):415-419.
35. Koempel JA. On the origin of tonsillectomy and the dissection method. *Laryngoscope* 2002; 112:1583-1586.

36. Lee KC, Bent JP, Dolitsky JN, et al. Surgical advances in tonsillectomy: report of a roundtable discussion. *Ear Nose Throat J* 2004; (suppl 3):83-4-13.
37. Van Den Akker EH, Hoes AW, Burton MJ, et al. Large international differences in (adeno) tonsillectomy rates. *Clin Otolaryngol* 2004; 29:161-164.
38. Beaty, MM, Funk GF, Karnell LH, et al. Risk factors for malignancy in adult tonsils. *Head Neck* 1998; 20(5): 399-403.
39. Discolo CM, Darrow DH, Koltai PJ. Infectious indications for tonsillectomy. *Pediatr Clin North Am* 2003; 50: 445-458.
40. Deutsch ES. Tonsillectomy and adenoidectomy. Changing indications. *Pediatr Clin North Am* 1996; 43(6):1319-1338.
41. Paradise JL, Bluestone CD, Colburn DK, et al. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics* 2002; 110:7-15.
42. Van Staaïj BK, van den Akker EH, van der Heijden GJMG, et al. Adenotonsillectomy for upper respiratory infections: evidence based? *Arch Dis Child* 2005; 90:19-25.
43. Van Staaïj BK, van den Akker EH, Rovers MM, et al. Effectiveness of adenotonsillectomy in children with mild symptoms of throat infections or adenotonsillar hypertrophy: open, randomized controlled trial. *Clin Otolaryngol* 2005; 0(1):60-63.
44. Mehanna H, Rejali D, Murray A. Suspending tonsillectomy: The effects on primary and secondary acute care in Scotland. *Scot Med J* 2004; 49:144-145.
45. Darrow DH, Siemens C. Indications for tonsillectomy and adenoidectomy. *Laryngoscope* 2002; 112:6-9.
46. Netser JC, Robinson RA, Smith RJ, et al. Value-Based Pathology. A cost-benefit analysis of the examination of routine and nonroutine tonsil and adenoid specimens. *Am J Clin Pathol* 1997; 108:158-165.
47. Alvi A, Vartanian J. Microscopic examination of routine tonsillectomy specimens: is it necessary? *Otolaryngol Head Neck Surg* 1998; 119:361-363.
48. Williams MD, Brown HM. The adequacy of gross pathological examination of routine tonsils and adenoids in patients 21 years old and younger. *Hum Pathol* 2003; 34(10):1053-1057.
49. Dohar JE, Bonilla JA. Processing of adenoid and tonsil specimens in children: a national survey of standard practices and a five-year review of the experience at the Children's Hospital of Pittsburgh. *Otolaryngol Head Neck Surg* 1996; 115:94-97.
50. Younis RT, Hesse SV, Anand VK. Evaluation of the utility and cost-effectiveness of obtaining histopathologic diagnosis on all routine tonsillectomy specimens. *Laryngoscope* 2001; 111:2166-2169.
51. Daneshbod K, Bhutta RA, Sodagar R. Pathology of tonsils and adenoids: a study of 15,120 cases. *Ear Nose Throat J* 1980; 59(11):466-467.

XXI. PERITONSILLAR ABSCESS

1. Harner SG. Peritonsillar, peripharyngeal, and deep neck abscesses. *Postgrad Med* 1975; 57(6):147-149.
2. Tewfik TL, Garni MA. Tonsillopharyngitis: clinical highlights. *J Otolaryngol* 2005; 34(suppl 1):S45-S49.
3. Scott PMJ, Dhillon RS, McDonald PJ. Cervical necrotizing fasciitis and tonsillitis. *J Laryngol Otol* 1994; 108(5):435-437.
4. Mitchelmore IJ, Prior AJ, Montgomery PQ, et al. Microbiological features and pathogenesis of peritonsillar abscesses. *Eur J Clin Microbiol Infect Dis* 1995; 14:870-877.
5. Fujimoto M, Aramaki H, Takano S, et al. Immediate tonsillectomy for peritonsillar abscess. *Acta Otolaryngol Suppl* 1996; 523:252-255.

XXII. ADENOID HYPERPLASIA

1. Lesmeister MJ, Bothwell MR, Misfeldt ML. Toll-like receptor expression in the human nasopharyngeal tonsil (adenoid) and palatine tonsils: A preliminary report. *J Pediatr Otolaryngol* 2006; 70:545-552.
2. Deutsch ES. Tonsillectomy and adenoidectomy. *Pediatr Otolaryngol* 1996; 43:1319-1338.
3. Richardson, MA. Sore throat, tonsillitis, and adenoiditis. *Med Clin North Am* 1999; 83(1):75-83.
4. Brodsky L, Koch J. Anatomic correlates of normal and diseased adenoids in children. *Laryngol* 1992; 102: 1268-1274.
5. Suzuki M, Watanabe T, Mogi G. Clinical, bacteriological, and histological study of adenoids in children. *Am J Otolaryngol* 1999; 20:85-90.
6. Fujiyoshi T, Watanabe T, Ichimiya I, et al. Functional architecture of the nasopharyngeal tonsil. *Am J Otolaryngol* 1989; 10(2):124-131.
7. Yasan H, Dogru H, Tuz M, et al. Otitis media with effusion and histopathologic properties of adenoid tissue. *Int J Pediatr Otorhinolaryngol* 2003; 67:1179-1183.
8. Gates GA, Muntz HR, Gaylis B. Adenoidectomy and otitis media. *Ann Otol Rhinol Laryngol Suppl* 1992; 155:24-32.
9. Kveton JF, Pillsbury HC, Saaski CT. Adenoiditis vs. adenoid hypertrophy. *Arch Otolaryngol* 1982; 108:315-318.
10. Hickey SA, Buckley JF, McCartney JC, et al. View from beneath: Pathology in Focus. Adenoidal hypertrophy as the presenting feature of HIV infection. *J Laryngol Otol* 1990; 104:58-60.
11. Shapiro NL, Strocker AM. Adenotonsillar hypertrophy and Epstein-Barr Virus in pediatric organ transplant recipients. *Laryngoscope* 2001; 111:997-1001.
12. Valtonen HJ, Blomgren EV, Qvarnberg YH. Consequences of adenoidectomy in conjunction with tonsillectomy in children. *Int J Pediatr Otorhinolaryngol* 2000; 53:105-109.
13. Buchinsky FJ, Lowry MA, Isaacson G. Do adenoids regrow after excision? *Otolaryngol Head Neck Surg* 2000; 123:576-581.
14. Darrow DH, Siemens C. Indications for tonsillectomy and adenoidectomy. *Laryngoscope* 2002; 112:6-10.
15. Van Staaïj Bak, van der Akker EH, Rovers MM, et al. Effectiveness of adenotonsillectomy in children with mild symptoms of throat infections or adenotonsillar hypertrophy: open, randomized controlled trial. *Clin Otolaryngol* 2005; 30(1):60-63.

XXIII. OBSTRUCTIVE SLEEP APNEA

1. Collop NA. Obstructive sleep apnea syndromes. *Semin Respir Crit Care Med* 2005; 26(1):13-24.
2. Magliocca KR, Helman JL. Obstructive sleep apnea. *JADA* 2005; 136:1121-1129.
3. Greenfeld M, Tauman R, DeRowe A, et al. Obstructive sleep apnea syndrome due to adenotonsillar hypertrophy in infants. *Int J Pediatr Otorhinolaryngol* 2003; 67(10): 1055-1060.
4. Bower CM, Richmond D. Tonsillectomy and adenoidectomy in patients with Down syndrome. *Int J Pediatr Otorhinolaryngol* 1995; 33(2):141-148.
5. Huang RY, Shapiro NL. Adenotonsillar enlargement in pediatric patients following solid organ transplantation. *Arch Otolaryngol Head Neck Surg* 2000; 126:159-164.
6. Schwab RJ. Genetic determinants of upper airway structures that predispose to obstructive sleep apnea. *Respir Physiol Neurobiol* 2005; 147(2-3):289-298.
7. Nishimura T, Suzuki K. Anatomy of oral respiration: morphology of the oral cavity and pharynx. *Acta Otolaryngol Suppl* 2003; 550:25-28.

8. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. *Arch Pediatr Adolesc Med* 2005; 159:775-785.
9. Caples SM, Gami AS, Somers VK. Obstructive sleep apnea. *Ann Intern Med* 2005; 142:187-197.
10. Yates DW. Adenotonsillar hypertrophy and cor pulmonale. *Br J Anaesth* 1988; 61:355-359.

XXIV. LOBULAR CAPILLARY HEMANGIOMA

1. Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. *Am J Surg Pathol* 1980; 4:471-479.
2. Epivatianos A, Antoniadis D, Zaraboukas T, et al. Pyogenic granuloma of the oral cavity: comparative study of its clinicopathological and immunohistochemical features. *Pathol Int* 2005; 55(7):391-397.
3. Toida M, Hasegawa T, Watanabe F, et al. Lobular capillary hemangioma of the oral mucosa: clinicopathological study of 43 cases with a special reference to immunohistochemical characterization of the vascular elements. *Pathol Int* 2003; 53(1):1-7.
4. Sato H, Takeda Y, Satoh M. Expression of the endothelial receptor tyrosine kinase Tie2 in lobular capillary hemangioma of the oral mucosa: an immunohistochemical study. *J Oral Pathol Med* 2002; 31:432-438.
5. Willies-Jacobo LJ, Issacs H Jr., Stein MT. Pyogenic granuloma presenting as a congenital epulis. *Arch Pediatr Adolesc Med* 2000; 154:603-605.
6. Espinoza I, Rojas R, Aranda W, et al. Prevalence of oral mucosal lesions in elderly people in Santiago, Chile. *J Oral Pathol Med* 2003; 32:571-575.
7. Silverstein LH, Burton CH Jr., Singh BB. Oral pyogenic granuloma in pregnancy. *Int J Gynaecol Obstet* 1995; 49(3):331-332.
8. Munoz M, Monje F, del Hoyo JRA, et al. Oral Angiosarcoma misdiagnosed as a pyogenic granuloma. *J Oral Maxillofac Surg* 1998; 56:488-491.
9. Ramirez JR, Seone J, Montero J, et al. Isolated gingival metastasis from hepatocellular carcinoma mimicking a pyogenic granuloma. *J Clin Periodontol* 2003; 30:926-929.
10. Lopez de Blanc S, Sambuelli R, Femopase F, et al. Bacillary angiomatosis affecting the oral cavity. Report of two cases and review. *J Oral Pathol Med* 2000; 29:91-96.
11. Monteil RA, Michiels JF, Hofman P, et al. Histological and ultrastructural study of one case of oral bacillary angiomatosis in HIV disease and review of the literature. *Eur J Cancer B Oral Oncol* 1994; 30(1):65-71.

XXV. CROHN DISEASE

1. Bozkurt T, Langer M, Fendel K, et al. Granulomatous tonsillitis, a rare extraintestinal manifestation of Crohn's disease. *Dig Dis Sci* 1992; 37(7):1127-1130.
2. Mones RL, Merrell N. Crohn's disease presenting as chronic purulent tonsillitis. *J Pediatr Gastroenterol Nutr* 1984; 3(3):475-477.
3. Stavropoulos F, Katz J, Guelmann M, et al. Oral ulcerations as a sign of Crohn's disease in a pediatric patient: a case report. *Pediatr Dent* 2004; 26:355-358.
4. Plauth M, Jenss H, Meyle J. Oral manifestations of Crohn's disease. *J Clin Gastroenterol* 1991; 13(1):29-37.
5. Riggio MP, Gibson J, Lennon A, et al. Search for Mycobacterium paratuberculosis DNA in orofacial granulomatosis and oral Crohn's disease tissue by polymerase chain reaction. *Gut* 1997; 41:646-650.

6. Dupuy A, Cosnes J, Revuz J, et al. Oral Crohn disease. *Arch Dermatol* 1999; 135:439-442.
7. Kalmar JR. Crohn's disease: orofacial considerations and disease pathogenesis. *Periodontology* 2000; 6:101-115.
8. Lee CYS, Tomich CE. Oral lesions in Crohn's disease: review of the literature with case report. *Hawaii Dent J* 1995; 26(6):11-12.
9. Rehberger A, Puspok A, Stallmeister T, et al. Crohn's disease masquerading as aphthous ulcers. *Eur J Dermatol* 1998; 8:274-276.
10. Scheper HJ, Brand HS. Oral aspects of Crohn's disease. *Int Dent J* 2002; 52(3):163-172.
11. Weiss JS, Gupta AK, Regezi J, et al. Oral ulcers and cobblestone plaques. *Arch Dermatol* 1991; 127(6):889-892.
12. Malins TJ, Wilson A, Ward-Booth RP. Recurrent buccal space abscesses: a complication of Crohn's disease. *Oral Surg Oral Med Oral Pathol* 1991; 72:19-21.
13. Mills CC, Amin M, Manisali M. Salivary duct fistula and recurrent buccal space infection: a complication of Crohn's disease. *J Oral Maxillofac Surg* 2003; 61:1485-1487.
14. Halme L, Meurman JH, Laine P, et al. Oral findings in patients with active or inactive Crohn's disease. *Oral Surg Oral Med Oral Pathol* 1993; 76:175-181.
15. Schnitt SJ, Antonioli DA, Jaffe B, et al. Granulomatous inflammation of minor salivary gland ducts: a new oral manifestation of Crohn's disease. *Hum Pathol* 1987; 18:405-407.
16. Alawi F. Granulomatous diseases of the oral tissues: differential diagnosis and update. *Dent Clin North Am* 2005; 49:203-221.
17. Onishi Y, Imai Y, Tojima H, et al. Systemic sarcoidosis with significant granulomatous swelling of the pharyngeal tonsil. *Int Med* 1998; 37:157-160.
18. Ferguson MM, MacFayden EE. Orofacial granulomatosis – a 10 year review. *Ann Acad Med Singapore* 1986; 15(3):370-377.
19. Sciubba JJ, Said-Al-Naief N. Orofacial granulomatosis: presentation, pathology and management of 13 cases. *J Oral Pathol Med* 2003; 32:576-585.
20. Khouri JM, Bohane TD, Day AS. Is orofacial granulomatosis in children a feature of Crohn's disease? *Acta Paediatr* 2005; 94(4):501-504.

XXVI. ECTOPIC THYROID

A. Lingual Thyroid

1. Rinkel RNPM, Manni JJ, Van der beek JMH. Ectopic thyroid tissue manifesting as a unique cause of an oropharyngeal mass. *Otolaryngol Head Neck Surg* 2001; 124(3):340-341.
2. Kumar PV, Akbari HMH, Arjmand F. Letters to the editor: Lingual thyroid diagnosed by fine needle aspiration cytology. *Acta Cytologica* 1996; 40(2):387-389.
3. Kumar R, Sharma S, Marwah A, et al. Ectopic goiter masquerading as submandibular gland swelling. *Clin Nucl Med* 2001; 26(4):306-309.
4. Soscia A, Guerra G, Cinelli MP. Parapharyngeal ectopic thyroid: the possible persistence of the lateral thyroid anlage. Clinical case report. *Surg Radiol Anat* 2004; 26:338-343.
5. Mysorekar VV, Dandekar CP, Sreevathsa MR. Ectopic thyroid tissue in the parotid salivary gland. *Singapore Med J* 2004; 45(9):437-438.
6. Maino K, Skelton H, Yeager J, et al. Benign ectopic thyroid tissue in a cutaneous location: a case report and review. *J Cutan Pathol* 2004; 31:195-198.

7. Yimaz F, Uzunlar AK, Sogutcu N. Ectopic thyroid tissue in the uterus. *Acta Obstet Gynecol Scand* 2005; 84(2):201–202.
8. Baughman RA. Lingual thyroid and lingual thyroglossal tract remnants. A clinical and histopathologic study with review of the literature. *Oral Surg Oral Med Oral Pathol* 1972; 34(5):781–799.
9. Bayram F, Kulahi I, Yuce K, et al. Functional lingual thyroid as unusual cause of progressive dysphagia. *Thyroid* 2004; 14(4):321–324.
10. Banna M, Lasjuanias P. The arteries of the lingual thyroid: angiographic findings and anatomic variations. *AJNR* 1990; 11:730–732.
11. Abdallah-Matta MP, Dubarry PH, Pessey JJ, et al. Lingual thyroid and hyperthyroidism: A new case and review of the literature. *J Endocrinol Invest* 2002; 25:264–267.
12. Thomas G, Hoilat R, Daniels JS, et al. Ectopic lingual thyroid: a case report. *Int J Oral Maxillofac Surg* 2003; 32:219–221.
13. Kansal P, Sakati N, Rifai A, et al. Lingual thyroid. Diagnosis and treatment. *Arch Intern Med* 1987; 147:2046–2048.
14. Fogarty D. Lingual thyroid and difficult intubation. *Anaesthesia* 1990; 45(3):251.
15. Neinas FW, Gorman CA, Devine KD, et al. Lingual Thyroid: Clinical characteristics of 15 cases. *Ann Int Med* 1973; 79:205–210.
16. Barthel A, Bornstein SR. Obstructive lingual thyroid. *N Engl J Med* 2005; 352:1.
17. Kalan A, Tariq M. Lingual thyroid gland: clinical evaluation and comprehensive management. *Ear Nose Throat J* 1999; 78(5):340–341, 345–349.
18. Barnes TW, Olsen KD, Morgenthaler TI. Obstructive lingual thyroid causing sleep apnea: a case report and review of the literature. *Sleep Med* 2004; 5(6):605–607.
19. Massine RE, Durning SJ, Koroscil TM. Lingual thyroid carcinoma: a case report and review of the literature. *Thyroid* 2001; 11(12):1191–1196.

B. Benign Thyroid Inclusions in a Lymph Node

1. Fliegelman LJ, Genden EM, Brandwein M, et al. Significance and management of thyroid lesions in lymph nodes as an incidental finding during neck dissection. *Head Neck* 2001; 23(10):885–891.
2. Butler JJ, Tulinius H, Ibanez ML, et al. Significance of thyroid tissue in lymph nodes associated with carcinoma of the head, neck or lung. *Cancer* 1967; 20:103–112.
3. Clark RL, Hickey RC, James JJ, et al. Thyroid cancer discovered incidentally during treatment for an unrelated head and neck cancer: review of 16 cases. *Ann Surg* 1966; 163(5):665–671.
4. Ibrahim NB, Milewski PJ, Gillett R et al. Benign thyroid inclusions within cervical lymph nodes: an alarming incidental finding. *Aust N Z J Surg* 1981; 51(2):188–189.
5. Fechner RE. Pathologic Quiz Case 1. *Arch Otolaryngol* 1984; 110:698–700.
6. Gerard-Marchant R. Thyroid follicle inclusions in cervical lymph nodes. *Arch Pathol* 1964; 77:633–637.
7. Meyer JS, Steinberg LS. Microscopically benign thyroid follicles in cervical lymph nodes. *Cancer* 1969; 24:302–311.
8. Ansari-Lari MA, Westra WH. The prevalence and significance of clinically unsuspected neoplasms in cervical lymph nodes. *Head Neck* 2003; 25(10):841–847.
9. Leon X, Sancho FJ, Garcia J, et al. Incidence and significance of clinically unsuspected thyroid tissue in lymph nodes found during neck dissection in head and neck carcinoma patients. *Laryngoscope* 2005; 115(3):470–474.
10. Kakudo K, Shan L, Nakamura Y, et al. Clonal analysis helps to differentiate aberrant thyroid tissue from thyroid carcinoma. *Hum Pathol* 1998; 29(2):187–190.
11. Rosai J, Carcangui ML, De Lellis RA. *Atlas of Tumor Pathology*. Washington, DC: Armed Forces Institute of Pathology, 1992:323.
12. Vassilopoulou-Sellin R, Weber RS. Metastatic thyroid cancer as an incidental finding during neck dissection: significance and management. *Head Neck* 1992; 14(6):459–463.

C. Ectopic Benign Thyroid Tissue in Nonlymphoid Tissues of the Head and Neck

1. Damiano A, Glickman AB, Rubin JS, et al. Ectopic thyroid tissue presenting as a midline neck mass. *Int J Pediatr Otorhinolaryngol* 1996; 34(1–2):141–148.
2. MacCormick J, Carpenter B. Pediatric intratracheal ectopic thyroid tissue: case study and review of the literature. *J Otolaryngol* 2005; 34(5):365–369.
3. Bowen-Wright HE, Jonklaas J. Ectopic intratracheal thyroid: an illustrative case report and literature review. *Thyroid* 2005; 15(5):478–484.
4. Soylu L, Kiroglu F, Ersoz C, et al. Intralaryngotracheal thyroid. *Am J Otol* 1993; 14(3):145–147.
5. Kumar R, Sharma S, Marwah A, et al. Ectopic goiter masquerading as submandibular gland swelling. *Clin Nucl Med* 2001; 26(4):306–309.
6. Yamauchi M, Inoue D, Sato H, et al. A case of ectopic thyroid in lateral neck associated with Graves' disease. *Endocr J* 1999; 46(5):731–734.
7. Wong RJ, Cunningham MJ, Curtin HD. Cervical ectopic thyroid. *Am J Otol* 1998; 19(6):397–400.
8. Rubinfeld S, Joseph UA, Schwartz MR, et al. Ectopic thyroid in the right carotid triangle. *Arch Otolaryngol Head Neck Surg* 1988; 114:913–915.
9. Morgan NJ, Emberton P, Barton RPE. The importance of thyroid scanning in neck lumps – a case report of ectopic tissue in the right submandibular region. *J Laryngol Otol* 1995; 109(7):674–676.
10. Block MA, Wylie JH, Patton RB, et al. Does benign thyroid tissue occur in the lateral part of the neck? *Am J Surg* 1966; 112:476–481.
11. Mysorekar VV, Dandekar CP, Sreevathsa MR. Ectopic thyroid tissue in the parotid salivary gland. *Singapore Med J* 2004; 45(9):437–438.
12. Rinkel RNPM, Manni JJ, Van der beek JMH. Ectopic thyroid tissue manifesting as a unique cause of an oropharyngeal mass. *Otolaryngol Head Neck Surg* 2001; 124(3):340–341.
13. Maino K, Skelton H, Yeager J, et al. Benign ectopic thyroid tissue in a cutaneous location: a case report and review. *J Cutan Pathol* 2004; 31:195–198.
14. Harach HR, Cabrerra JA, Williams ED. Thyroid implants after surgery and blunt trauma. *Ann Diagn Pathol* 2004; 8(2):61–68.
15. Kumar PV, Akbari HMH, Arjmand F. Letters to the editor: Lingual thyroid diagnosed by fine needle aspiration cytology. *Acta Cytologica* 1996; 40(2):387–389.

Noninfectious Vesiculoerosive and Ulcerative Lesions of the Oral Mucosa

Susan Müller

Department of Pathology and Laboratory Medicine and Department of Otolaryngology-Head & Neck Surgery, Emory University School of Medicine, Atlanta, Georgia, U.S.A.

I. INTRODUCTION

Many conditions that affect the oral mucosa along with other mucosal sites are either autoimmune or immunologically mediated. They include pemphigus, mucous membrane pemphigoid (MMP), lichen planus, aphthous stomatitis, linear IgA, bullous dermatitis, dermatitis herpetiformis, and epidermolysis bullosa acquisita (EBA). The clinical manifestations include vesicles, bullae, erosions, and ulcers. Often-times, both the clinical and histopathological features of some of these conditions overlap, thereby making even more sophisticated methods necessary for accurate diagnosis (Table 1). Because both the clinical presentation and the immunology of the disease can be critical in making the correct diagnosis, both areas are addressed, along with the pathology of vesiculoerosive and ulcerative lesions of the oral mucosa.

II. PEMPHIGUS

A. Introduction

The condition known as *pemphigus* refers to a group of related diseases that are characterized clinically by blistering, microscopically by acantholysis, and immunologically by autoantibodies directed against specific proteins in the epidermal (epithelial) cell membrane resulting in the loss of cell-cell adhesion. There are three major subtypes of pemphigus—pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus. This section will be limited to discussing pemphigus subtypes that routinely have an oral mucosal component.

B. Pemphigus Vulgaris

Introduction

PV is an autoimmune intraepithelial blistering disorder affecting both skin and mucous membranes that usually occurs in patients aged between 40 and 60 years. However, the age range is broad and PV has been described in children. Men and women are

equally affected by the disease. PV has a worldwide case incidence between 0.1 and 3.2 cases per 100,000 individuals per year in the general population and occurs in all ethnic and racial groups, with an increased incidence among persons of Mediterranean descent and Ashkenazi Jews (1).

Studies of patients with PV indicate a histocompatibility antigen (HLA) link to disease susceptibility. There is a strong HLA concordance, and reports show that alleles of HLA-DR4, HLA-DR14, and HLA-B15 confer susceptibility to PV in different ethnic groups (2).

Clinical Presentation

PV originates in the oral mucosa membranes in 50% to 70% of patients, and more than 90% of patients will have oral involvement at some time during the course of their disease (3). Mucosal PV may precede cutaneous PV by an average of five months or may be the sole manifestation of the disease. Only 10% to 50% of patients demonstrate skin lesions initially. Although the oral mucosa is most commonly affected, all mucosae may be involved, including the pharynx, larynx, esophagus, cervix, urethra, anal mucosa, and conjunctiva.

The primary lesion is a flaccid blister, and these lesions coalesce to form bullae in the mouth. Red, painful erosions, most commonly on the buccal, palatine, and gingival mucosa, are seen (Fig. 1). In severe cases, the entire mucosal surface can be involved. When the oropharynx is involved, swallowing can become difficult and extension to the pharynx and larynx may present as hoarseness. Esophageal involvement is uncommon with presenting symptoms of odynophagia and dysphagia.

PV may remain limited to the oral cavity for several weeks to more than one year before skin involvement. Interestingly, oral lesions may also be the last to clear. There are other vesiculoerosive lesions that may have a presentation in the oral cavity similar to PV, including bullous pemphigoid, erosive lichen planus, lupus erythematosus (LE), erythema multiforme (EM), Behçet's disease, necrotizing gingivostomatitis, idiopathic forms of desquamative gingivitis, and ulcerative stomatitis. In view of the diverse

Table 1 Comparative Features of Oral Vesiculoerosive and Ulcerative Diseases

Disease	Clinical features	Histopathological features	Direct immunofluorescence	Indirect immunofluorescence
Pemphigus vulgaris	3rd to 4th decade, oral lesions in >50% of patients, may be presenting symptom. Flaccid blisters on normal or erythematous skin	Suprabasal acantholysis of keratinocytes with "tombstone" appearance of basal cells	Positive intercellular for IgG or IgM and C3	Circulating autoantibodies often correlate with disease activity
Pemphigus vegetans	Pustules or bullae followed by formation of verrucous vegetations. Oral vegetations unusual	Similar to pemphigus vulgaris with additional features of intraepidermal eosinophilic abscesses, hyperkeratosis, and papillomatosis	Similar to pemphigus vulgaris	Serum autoantibodies can sometimes be detected
Paraneoplastic pemphigus	Mucous membrane involvement universal, erosive conjunctivitis, associated malignancy	Supra- or subbasal acantholysis, necrosis of individual keratinocytes and vacuolar interface change	Positive intercellular IgG with or without complement	Serum autoantibodies (use transitional type epithelium as substrate)
Bullous pemphigoid	6th–7th decade with tense blisters on normal or erythematous skin. Oral lesions rarely presenting symptom	Subepithelial blister with a mild inflammatory infiltrate in dermis	IgG, C3 bound at BMZ	Circulating IgG BMZ antibodies found in 70% of patients. Titer does not correlate with disease activity
Mucous membrane pemphigoid	6th–7th decade, blistering disease of mucosal surfaces, oral involvement nearly universal. Ocular lesions can lead to symblepharon formation	Similar to bullous pemphigoid	IgG and C3, may also identify IgA and IgM, bound at BMZ	The incidence of circulating antibodies reported in 5–90% of patients, no correlation with disease activity
Lupus erythematosus (oral findings)	Presents in 4th decade, mainly affects females, Erythematous, discoid or ulcerative oral lesions	Basal vacuolization, dyskeratosis with superficial and deep perivascular infiltrate	IgG, IgA, IgM, C3 along basement membrane	Not specific
Oral lichen planus	Presents in 5th–6th decade, lace-like reticular pattern. Erosive form shows central ulcerations	Basal cell liquefaction, Civatte bodies, band-like inflammation of lymphocytes at the epithelium-connective tissue interface	Not specific, shaggy band of fibrinogen present at BMZ	Not specific
Erythema multiforme	3rd–4th decade, target lesions on trunk and extremities, ulcerated oral mucosa, hemorrhagic crusting of erosions on lips	Interface dermatitis with basal vacuolization and dyskeratotic cells scattered throughout the epidermis and mucosa	Not specific	Not specific

Abbreviation: BMZ, basement membrane zone.

number of oral diseases that can mimic PV, obtaining tissue for microscopic examination and immunofluorescence is required for definitive diagnosis.

Pathology

Suprabasal bullae formation occurs in PV. The earliest change is intercellular edema within the epithelium. The subsequent acantholysis leads to the formation of clefts and then of bullae immediately above the basal

layer (Fig. 2). The single row of basal cells, many of which are separated from each other, have a cuboidal shape giving the characteristic "tombstone" appearance (Fig. 2). Irregular upward growth of papillae, which are lined by a single row of basal cells and downward proliferation of strands of epithelial cells, in the spaces between the papillae are observed (Fig. 3).

During the early bullous phase of PV, there is little or no inflammation. At times, eosinophils invade the epidermis before acantholysis, and this has been



Figure 1 Pemphigus vulgaris involving the soft palate presenting as an irregular ulceration. The upper portion of the lesion represents the roof of the collapsed bulla.

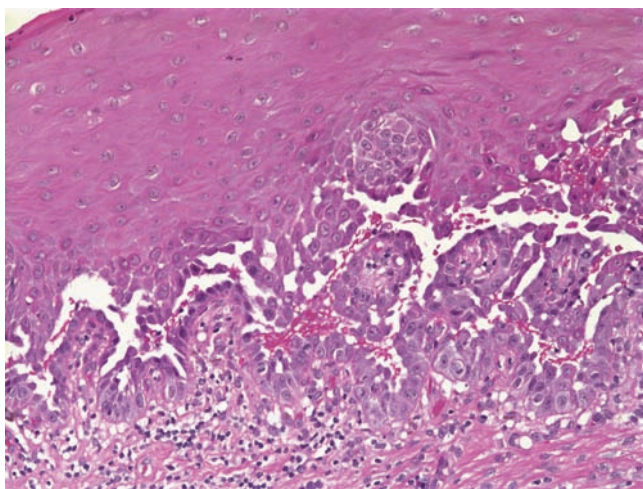


Figure 2 Pemphigus vulgaris. A suprabasal separation is present. A mild amount of inflammation is present in the underlying lamina propria.

referred to as eosinophilic spongiosis (1). Because of the loss of cohesion, acantholytic cells, called “Tzanck cells,” become round, swollen, and hyperchromatic (Fig. 3). This feature is useful in identifying PV in exfoliative cytological preparations.

Immunopathology

The use of direct immunofluorescence can confirm the diagnosis of PV. Patients with active disease will have immunoglobulin G (IgG) deposits in the intercellular space of lesional and clinically normal perilesional skin (4). The best results for direct immunofluorescence are obtained by biopsy of fresh perilesional tissue or tissue submitted in Michel’s solution. A homogeneous staining of the intercellular space at all levels of the epidermis is seen (Fig. 4). This distinct

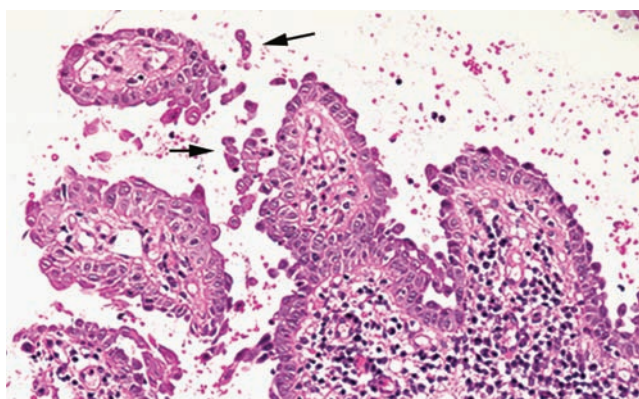


Figure 3 Pemphigus vulgaris demonstrating the irregular papillary projections of the submucosa. The overlying epithelium is absent, with the exception of the basal cells. Round and swollen acantholytic cells, also called Tzanck cells, can be seen (arrows).

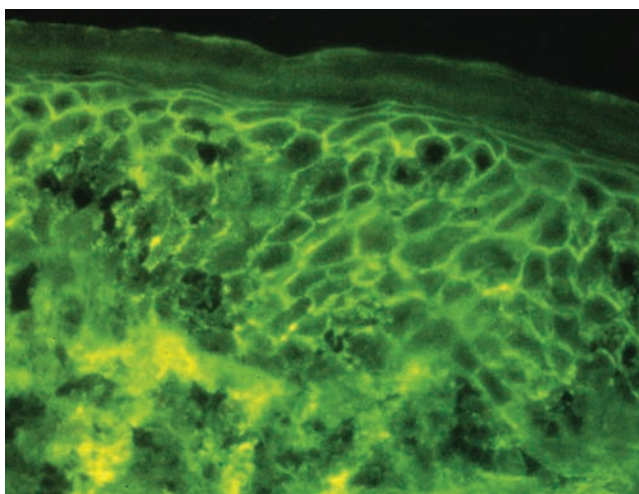


Figure 4 Direct immunofluorescence of perilesional skin in pemphigus vulgaris. Note the IgG deposits in the intercellular desmosomal areas. *Abbreviation:* IgG, immunoglobulin G.

staining pattern is seen in all pemphigus variants except in some cases of pemphigus foliaceus, in which the fluorescence may be limited to the site of the blister. In addition to IgG deposits, complement component C3 may have deposits in a similar pattern to IgG. Intercellular space staining with IgA is characteristic of IgA pemphigus, which shares clinical and microscopic findings of pemphigus foliaceus and subcorneal pustular dermatosis.

Indirect immunofluorescence studies of serum from patients with PV can be helpful in confirming the disease as well as in differentiating PV from other related bullous diseases. Eighty to ninety percent of patients demonstrate circulating IgG antibodies against keratinocyte cell surface. Monkey esophagus

is the best substrate to use for assay of indirect immunofluorescence. Generally, antibody titers correlate with disease activity; however, false-positive results have been reported (1,4).

Immunology

Autoantibodies in the serum of patients with PV react against desmosomes, specifically the antigens, desmoglein 3 (DG3) and desmoglein 1 (DG1) in the basement membrane zone (BMZ). DG3 is a 130-kD desmosomal cadherin involved in cell-cell adhesion of keratinocytes. DG1 is a 160-kD antigen that reacts to pemphigus foliaceus. Studies have demonstrated that binding of PV antibodies to DG3 antigen causes loss of intercellular adhesion mechanisms, thereby inducing acantholysis and blister formation (2). Enzyme-linked immunosorbent assays (ELISA) have shown that PV can be further divided into a mucosal dominant type reactive with only DG3 and a mucocutaneous type reactive to both DG3 and DG1 (5).

Treatment and Prognosis

Prior to the advent of systemic corticosteroids, PV was associated with a high morbidity and mortality rate. Treatment of PV consists of local and systemic therapy, depending on the disease location and severity. Adjuvant immunosuppressants are used for their steroid-sparing effect, including methotrexate, azathioprine, cyclophosphamide, and cyclosporine. Drugs with an anti-inflammatory effect such as minocin, dapsone, or tetracycline have been successfully used in the treatment of PV. Patients resistant to other therapies have been treated with plasmapheresis or high-dose intravenous Igs. The duration of treatment is variable. The average time to achieve complete remission is reported from 2 to 10 years with complete remission highest in patients who initially present with mild disease and have a rapid response to treatment. Mortality from PV is about 6%, mainly due to complications from the long-term immunosuppressive therapy. Systemic infections are the most common cause of death of patients with PV who are receiving steroid therapy.

C. Pemphigus Vegetans

Pemphigus vegetans is an uncommon form of PV occurring in 1% to 2% of pemphigus cases (6). Two types of pemphigus vegetans are seen: the Neumann type and the Hallopeau type (6). The Neumann type is similar to PV, differing by having the denuded skin heal with verrucous vegetations that can be studded initially with small pustules. In the Hallopeau type (pyodermitis vegetans), pustules rather than bullae are the primary lesion. The pustules are followed by verrucous vegetations that gradually extend peripherally, particularly in the intertriginous area. Oral lesions are present in almost all patients with pemphigus vegetans, although oral vegetations are unusual. Vegetations can be seen along the lip vermillion, and nasal involvement is frequent. Cerebriform (scrotal) tongue

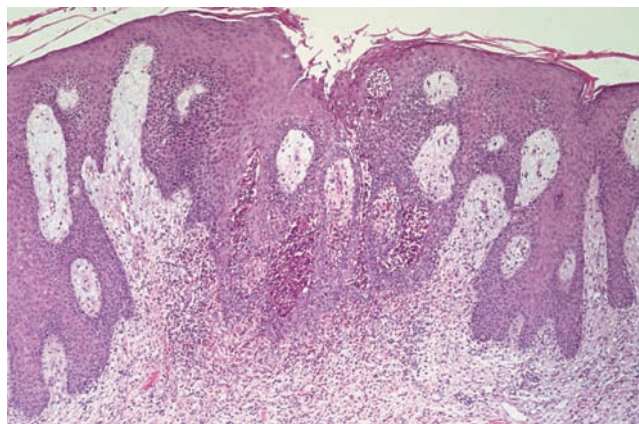


Figure 5 Pemphigus vegetans. Prominent acanthosis with intraepidermal abscesses consisting of eosinophils can be seen.

has been reported to be a characteristic feature of pemphigus vegetans (7). Fujimoto et al. reported a patient with the Hallopeau type who complained of deafness, otalgia, and facial nerve paralysis though was due to pressure of the facial nerve from vegetations in the middle ear and external auditory canal (8).

Pathology

The early lesions of the Neumann type, consisting of bullae and denuded areas, show the same histological picture as that seen in PV. Eosinophilic spongiosis is a more prominent feature in pemphigus vegetans. The pustules seen in the early vegetations are filled with eosinophils. These intraepithelial abscesses filled with eosinophils are highly diagnostic of pemphigus vegetans. Older vegetations demonstrating papillomatosis and hyperkeratosis are not diagnostic.

In the Hallopeau type, the pustules show acantholysis and the formation of clefts in a suprabasal location. Within these clefts are numerous eosinophils and acantholytic epidermal cells (Fig. 5). Early vegetating lesions show intraepidermal eosinophilic abscesses that are more numerous and larger than those seen in the Neumann type. Late vegetations of the Hallopeau type are histologically similar to the Neumann type.

Immunopathology

Pemphigus vegetans, being a subtype of PV, shows similar immunopathology on direct immunofluorescence of perilesional tissue. Autoantibodies in patients with pemphigus vegetans target both DG1 and DG3 (5).

D. Paraneoplastic Pemphigus

Sporadic cases of patients with neoplasms who also presented with blistering and erosive mucocutaneous lesions have been reported (9). Additionally, these patients have had high titers of "pemphigus-like" anti-cell-surface autoantibodies (9). These antibodies



Figure 6 Paraneoplastic pemphigus presenting with extensive ulcerations of the tongue. The lips also show multiple ulcerations with hemorrhagic crusting similar to erythema multiforme. *Source:* Courtesy of Dr. Carl M. Allen.

are distinct from those present in patients with PV and pemphigus foliaceus. In 1990, Anhalt et al. defined paraneoplastic pemphigus (PNP) as a distinct entity and developed specific diagnostic criteria (10).

Mucous membrane involvement, particularly the oral mucosa, is a consistent finding in PNP. All reported cases of PNP have painful blisters and erosive mucosa involving labial, gingival, buccal, and lingual mucosa and in 45% of reported cases was the initial manifestation (Fig. 6) (9). Mucosae of the oropharynx, nasopharynx, and hypopharynx have also been involved in some cases. Erosive conjunctivitis with subsequent scarring and symblepharon formation has occurred in many patients (11).

Cutaneous manifestations of PNP include polymorphous skin eruptions, with papular lesions progressing to blisters and erosions (10). Other lesions appear as erythematous areas with central vesicles, similar to target lesions of EM. Typically, the lesions affect the trunk, extremities, and palms and soles.

Both malignant and benign neoplasms have been associated with PNP. Hematological malignancies or disorders account for 84% of all reported cases of PNP (9–12). Epithelial malignancies account for 8.6% of cases, and sarcomas account for 6.4%. A known malignancy prior to the eruption of PNP is noted in about two-thirds of cases. PNP associated with malignancy is refractory to treatment, and the patients usually have a rapidly fatal course. Mucosal ulcerations do not respond to treatment with high-dose corticosteroids and immunosuppressive medications, although some patients have had clearing of cutaneous lesions (12).

Pathology

Light microscopy of biopsy specimens from patients with PNP can show a histological picture similar to PV. Individual cell necrosis of keratinocytes, acantholysis, and a vacuolar interface change, similar to EM, has been reported to be a predominant microscopic feature (13). At times, a subbasal, rather than a suprabasal,

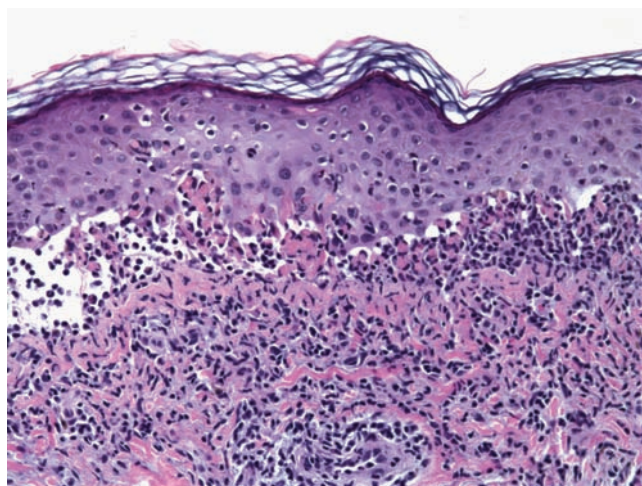


Figure 7 Paraneoplastic pemphigus, oral mucosa. A subbasal separation with hydropic degeneration of the basal cells overlying a mild chronic inflammatory cell infiltrate is seen.

separation can be observed (Fig. 7) (14). Su et al. reported a case of PNP in a patient with chronic lymphocytic leukemia in whom one biopsy specimen revealed features of both PV and bullous pemphigoid, along with necrotic keratinocytes and hydropic degeneration of the basal cells (14).

Immunopathology

With direct immunofluorescence, testing of perilesional skin or mucosa show intercellular epidermal IgG deposits and complement, with or without granular linear complement deposition along the BMZ (4).

Indirect immunofluorescence using sera of PNP patient against human epidermis or monkey esophagus are indistinguishable from the cell surface binding seen in PV or foliaceus. However, PNP does differ from other types of pemphigus in that the autoantibodies also bind to simple, columnar, and transitional epithelium. Rodent bladder epithelium substrate, human respiratory tract, colon, and small bowel epithelia, all have given consistent cell surface binding in patients with PNP (10). In all cases of PNP, the antibody class responsible for cell surface binding on indirect immunofluorescence is IgG.

Immunology

Five polypeptides can be consistently immunoprecipitated from the sera of patients with PNP (5). The polypeptides identified are 250-kD (desmoplakin I), 230-kD (bullous pemphigoid antigen), 210-kD (desmoplakin II), 190-kD (periplakin), and 170-kD (envoplakin). This polypeptide complex is not seen in other pemphigus types. Desmoplakins are structural proteins found in all epithelia associated with the cytoplasmic plaque at the desmosome cellular junction. This may account for the ability of PNP sera to react with

numerous types of epithelia. This immunoprecipitation profile is the most consistent laboratory finding in PNP.

Diagnosis

Anhalt et al. suggested five specific criteria to define PNP (10). Camisa and Helms proposed a revision dividing criteria into major and minor signs. Major signs include painful mucosal erosions and a polymorphous skin eruption, with papular lesions progressing to blisters and erosive lesions; immunoprecipitation of a complex of four proteins from keratinocytes by these antibodies; and concurrent internal neoplasia. Minor signs include histological evidence of epidermal acantholysis and interface changes; epidermal and BMZ deposition of IgG, as seen by direct immunofluorescence; and serum autoantibodies that bind to rat bladder epithelium on indirect immunofluorescence (15). Three major or two major and two minor signs are required for the diagnosis of PNP.

Clinical differential diagnosis of PNP can include PV, bullous pemphigoid, EM, and MMP. Drug-induced pemphigus, a rare disease, must also be considered. Evaluation of biopsies by light microscopy and direct immunofluorescence of serum and, in some cases, immunoprecipitation of a complex of four proteins, are required to confirm the diagnosis of PNP. Repeat testing, including additional biopsies, and direct and indirect immunofluorescence are often needed to arrive at a final diagnosis.

E. Drug-Induced Pemphigus

Many drugs have been reported to induce pemphigus on rare occasions (16,17). The clinical and histological features reported are quite variable, with the only consistent finding being epidermal acantholytic lesions related to the intake of a certain drug. Oral ulcerations are a common feature of drug-induced pemphigus. Penicillamine, used in the therapy of rheumatoid arthritis, progressive systemic sclerosis, and Wilson's disease, has reportedly been the causative agent of drug-induced pemphigus in 7% of patients taking this drug for longer than six months (16). Other drugs reported to cause pemphigus include captopril, rifampin, pyrazolone derivatives, thiopronin, pyritinol, and penicillin (16).

Most patients with drug-induced pemphigus experience disease regression when the medication is discontinued. In this group of patients, the disease is thought to be directly induced by the drug, usually one containing sulfhydryl groups and the prognosis is quite good. In another group of patients, the disease was believed to have been triggered by a nonsulfhydryl medication, which persists even after the medication was discontinued (16). This group of patients has a more protracted disease course, similar to patients with idiopathic pemphigus. In this group of patients, it has been postulated that genetic factors are also responsible. Studies have shown that patients with drug-induced pemphigus and idiopathic pemphigus share the same HLA alleles.

III. PEMPHIGOID

A. Bullous Pemphigoid

Bullous pemphigoid is a subepidermal blistering disease characterized by the deposition of autoantibodies at the BMZ. Bullous pemphigoid affects mostly the elderly population, with most patients older than 60 years. No definitive sex, racial, or ethnic tendency is seen.

Clinical Presentation

The development of tense blisters on either normal-appearing skin or, at times, on an erythematous base is the characteristic lesion. After the blisters rupture, they become flaccid and result in an eroded area. These blisters can range in size from small vesicles to large bullae many centimeters in diameter. Unless complicated by infection, most blisters will heal without scarring. Pruritus without skin findings may be an early symptom for some patients. Patients experiencing pruritus with absence of skin lesions may develop blistering lesions of bullous pemphigoid from one month to four years later (1).

Bullous pemphigoid can affect the oral mucous membranes in up to 40% of patients, but it is rarely the presenting symptom (2). In addition, these mucosal lesions are limited to the oropharynx. This presentation is very different from MMP, in which oral mucosal lesions are the primary location.

Pathology

The typical microscopic feature of tissue obtained from the perilesional margin of a bulla reveals a subepidermal blister (Fig. 8). A modest number of inflammatory cells, composed chiefly of eosinophils, but also containing lymphocytes, histiocytes, and neutrophils, may be present in the dermis or lamina

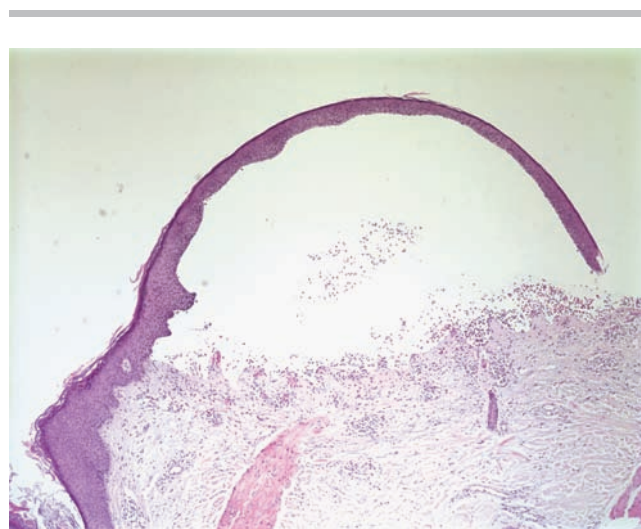


Figure 8 Bullous pemphigoid. A bulla is seen from the subepithelial detachment of the epidermis from the dermis.

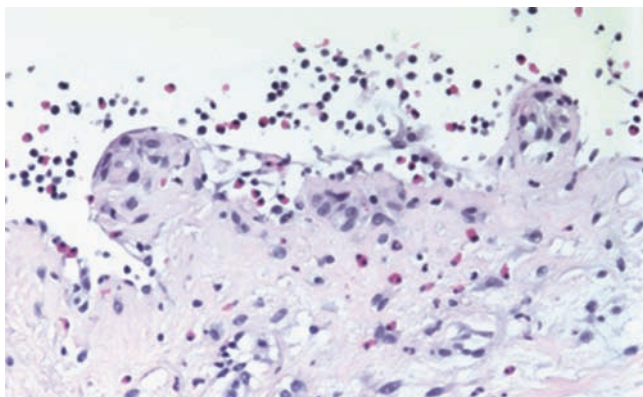


Figure 9 Bullous pemphigoid. Within the blister, eosinophils are prominent along with fibrin.

propria (Fig. 9). Blisters that arise on an erythematous base show more extensive accumulations of inflammatory cells. Within the bullae, eosinophils tend to predominate.

Immunopathology

Linear deposits of IgG, with IgG4 subclass predominance, and C3 at the BMZ are observed by direct immunofluorescence in most patients with bullous pemphigoid (3). Linear deposits of IgM, IgA, and IgE may also be present in some patients. This immunofluorescence pattern is not specific for bullous pemphigoid and is seen in MMP, EBA, herpes gestationis, and bullous systemic LE.

Unlike MMP, circulating IgG anti-BMZ antibodies are detectable in about 70% of bullous pemphigoid patients by indirect immunofluorescence (3). There is no correlation between antibody titer and severity of disease. Because circulating IgG antibodies directed against the basement membrane may also be seen in EBA, herpes gestationis, and MMP, special studies are, at times, needed to diagnose bullous pemphigoid.

When using routine direct immunofluorescence, the use of patient skin, split in vitro with 1-M NaCl, can help delineate these disease processes. Incubation of skin in 1.0 mol/L NaCl separates the BMZ through the lamina lucida separating the skin. The IgG deposits in bullous pemphigoid bind only on the epidermal side of the separation or both the epidermal and dermal sides, whereas the same antibodies bind to the dermal side in skin from patients with EBA.

Immunology

Patients with bullous pemphigoid have a circulating antigen, BP-antigen (BPAG1), a 230-kD polypeptide that is located intracellularly, associated with the hemidesmosome (1,4). Another BP-antigen, a 180-kD (BPAG2) protein is a transmembrane protein of the basal keratinocyte and upper lamina lucida (1,4). Some of the BP antibodies are complement activating and appear to play a very important pathogenic role

in bullous pemphigoid. The autoantibodies bind to the BP-antigen and activate the complement cascade. Inflammatory mediators are produced in the lamina lucida, including the anaphylatoxins C3a and C4a (4). Subsequent mast-cell activation and degranulation occurs, with release of numerous inflammatory mediators. Neutrophils and eosinophils migrate to the region of the basement membrane and then release their own inflammatory mediators, including enzymes responsible for the destruction of the dermal-epidermal junction. The final result is subepidermal blister formation.

Treatment and Prognosis

Unlike PV, bullous pemphigoid is rarely life threatening, even without treatment. Most patients with generalized disease are treated with systemic immunosuppressive therapy including corticosteroids, dapsone, and azathioprine (5). Many patients with bullous pemphigoid experience spontaneous remission of their disease two to three years after initial presentation.

B. Mucous Membrane MMP (Cicatricial Pemphigoid)

MMP is a chronic blistering disease affecting mainly the mucous membranes and occasionally the skin. Cicatricial refers to the scarring that can result particularly when the conjunctival mucosa is involved.

The exact incidence and prevalence of MMP is unknown, but it is less frequently diagnosed than bullous pemphigoid. MMP usually affects the middle-aged or elderly, with the average age of onset of 66 years (6). Women are affected more frequently than men by a ratio of 1.5 to 2:1.

Clinical Presentation

Oral mucosal involvement is the most consistent feature of MMP and occurs in almost all patients. Gingival involvement is seen in 64% of oral cases and presents as a desquamative gingivitis (Fig. 10) (2).



Figure 10 Mucous membrane pemphigoid presenting as desquamative gingivitis. The gingiva is erythematous, and the surface mucosa can be removed with ease. A similar clinical picture can sometimes be seen with pemphigus vulgaris or lichen planus.

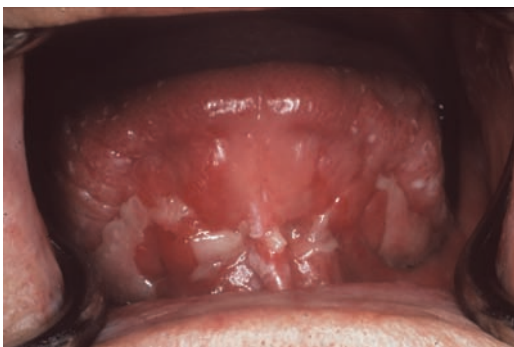


Figure 11 Mucous membrane pemphigoid occurring on the ventral surface of the tongue. The white, necrotic area represents the collapsed, but not yet detached, bulla.

Mild cases show erythema and edema of the gingiva, whereas more severe cases show blister formation and desquamation of the gingiva, resulting in erosions and ulcerations. The facial gingiva is involved more often than the lingual or palatal gingiva. A positive Nikolsky sign, where induced trauma can elicit a blister or bullae in clinically normal mucosa, is often seen in MMP. Although up to half of the patients who present clinically with desquamative gingivitis have or will eventually develop MMP, other cases may represent erosive lichen planus, or less likely, PV. Some cases of desquamative gingivitis without a specific diagnosis may represent a mucosal reaction to irritation (2).

MMP also involves in order of frequency, the buccal mucosa, palate, alveolar ridge, tongue, and lower lip (Fig. 11). In these areas, lesions appear as vesicles that rupture to leave erosions. The ulcerated lesions can be painful and may persist for weeks if not treated. Most erosions heal without scarring, however some scarring can result, appearing as a white, reticulated pattern resembling lichen planus. In severe cases, adhesions may form.

Ocular involvement is a serious complication of MMP and may occur in up to 37% of patients who have oral involvement (7). The earliest change is chronic conjunctival irritation, which may be unilateral or bilateral. Patients report a burning or a foreign body sensation and complain of dryness. As the disease progresses, ulcerations can be seen and further scarring occurs. Attempts at healing lead to fibrous adhesions that fuse the bulbar (scleral) and palpebral conjunctiva (Fig. 12) (8). These adhesions are called symblepharons. If the disease progresses, the conjunctiva can contract, inverting the eyelid margins (entropion). This causes the eyelashes to rub against the cornea (trichiasis). Further corneal injury may result in eventual blindness. Numerous other conditions can mimic ocular cicatricial pemphigoid, including linear IgA disease, dermatitis herpetiformis, Sjögren's syndrome, infection, and drug-induced conditions (9).

Although uncommon, when MMP involves the larynx, airway obstruction may result from bullae

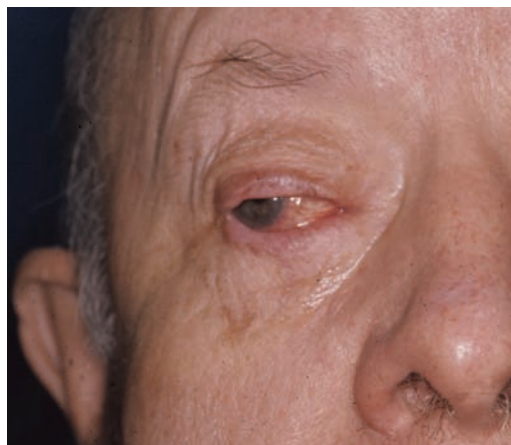


Figure 12 Mucous membrane pemphigoid. A patient with ocular involvement showing conjunctival inflammation and symblepharon formation.

formation. Involvement of the vocal cords may lead to dysphonia or hoarseness. If untreated, severe laryngeal lesions may lead to scarring with stenosis.

Both the nasopharynx and the esophagus can be involved in MMP. Patients with esophageal involvement may complain of dyspepsia or dysphagia. A complication of untreated esophageal lesions, which ulcerate and scar, is esophageal stenosis.

Other mucosal sites affected by MMP involve the anus, rectum, and vagina. Skin involvement is variable (10–43%) and clinically differs in presentation from patients with bullous pemphigoid (6). One type of eruption seen is a generalized bullous eruption similar to bullous pemphigoid, but of short duration, which allows differentiation from patients with bullous pemphigoid with oral lesions. Another type of skin lesions seen in MMP is recurrent blisters confined to a limited area, usually the head and neck, or skin adjacent to affected mucosa. These tense vesicles rupture, leading to erosions that may heal with scarring in one-third of cases (6).

Pathology

Examination of perilesional tissue reveals a subepithelial split, with a mild, chronic inflammatory cell infiltrate that consists of lymphocytes, plasma cells, eosinophils, and neutrophils (Fig. 13). Mucosal lesions often consist predominately of lymphocytes and plasma cells.

Immunopathology

Direct immunofluorescence of lesional and perilesional tissue from affected patients show a continuous linear band at the BMZ of fixed IgG or complement (Fig. 14). Primarily, both IgG and C3 are present, occasionally in association with IgM and IgA (3).

Unlike bullous pemphigoid, the presence of circulating anti-BMZ antibodies in the sera of patients

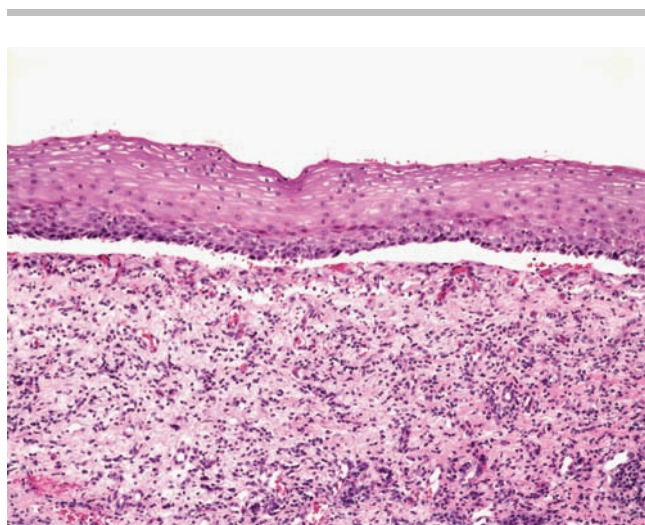


Figure 13 Mucous membrane pemphigoid. Characteristic subepithelial clefting is evident. The lamina propria contains a moderate chronic inflammatory cell infiltrate.

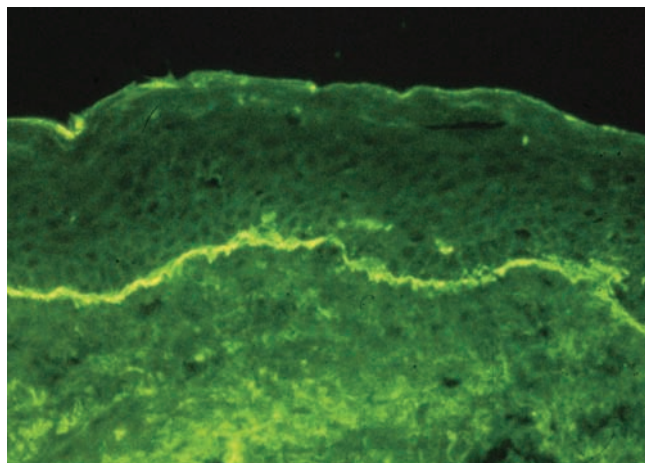


Figure 14 Direct immunofluorescence of perilesional tissue from a patient with mucous membrane pemphigoid. A continuous linear band of IgG is seen at the basement membrane zone. *Abbreviation:* IgG, immunoglobulin G.

with MMP are difficult to confirm. Various studies have reported circulating antibodies from 5% to 90% of affected patients (3,9). Use of salt-split human skin and mucosa as a substrate increases the sensitivity of indirect immunofluorescence, although the binding patterns are not disease specific (6). No correlation between circulating antibody titers and severity of disease is present in MMP.

Immunology

The precise pathogenic mechanisms of MMP are not completely understood. This is due to the lack of

disease-specific circulating antibodies in all patients. Studies of patients with circulating antibodies show antibodies specific for the hemidesmosomal proteins BPAG1 or BPAG2, similar to bullous pemphigoid. Other studies showed that some patients with MMP have autoantibodies against an anchoring filament protein, laminin 5, called epiligrin (5).

Differential Diagnosis

When a patient presents with mucosal ulcers, a biopsy of the blister or perilesional tissue should be performed for microscopic examination. Other diseases that present histologically as a subepithelial separation include linear IgA disease and EBA. Direct immunofluorescence is useful to distinguish between these conditions. If the deposition along the BMZ is predominantly IgA, then the diagnosis of linear IgA should be suspected.

EBA presents as an acquired subepidermal blistering disease characterized by a combination of blisters, erosions, scars, milia, and dyspigmentation of the skin (10). Involvement of the mucous membranes, including oral, pharyngeal, laryngeal, nasal, conjunctival, esophageal, and genital, are clinically similar to MMP. In EBA, the production of autoantibodies to the epithelial basement membrane protein type VII collagen is distinct and permits differentiation from other subepidermal blistering diseases (5). When EBA is suspected, using 1.0-mol NaCl-split perilesional tissue, which induces bullae formation, is helpful. The IgG autoantibodies will be seen on the floor of the induced bullae in EBA (corresponding to lamina densa), whereas in MMP, the IgG deposits are seen on the roof of the bullae (corresponding to lamina lucida) (3).

The reader is referred to specialty texts in dermatology for an in-depth discussion of linear IgA disease and EBA.

Treatment and Prognosis

Therapy for MMP depends on disease severity. Patients should be screened by an ophthalmologist, even in the absence of ocular lesions, to obtain a baseline examination of the conjunctivae. In limited oral disease, the application of corticosteroids as either a rinse or a topical form several times a day will control the lesions. Once the lesions regress, the corticosteroids can be discontinued, although recurrences are common. When extensive oral lesions are present or ocular involvement is seen, systemic therapy is required. Dapsone, a sulfanilamide drug derivative, has reportedly been effective in treating MMP. Systemic corticosteroids, often in conjunction with immunosuppressive drugs, such as cyclophosphamide, have also been used.

Patients with ocular scarring who are in complete remission may benefit from cryotherapy ablation. It is important to ascertain that the disease is in complete remission, for surgery can cause an exacerbation of the disease, with consequent corneal ulceration and blindness (7). Surgical correction of laryngeal or esophageal stenosis is also contraindicated in a patient with active disease.

IV. LUPUS ERYTHEMATOSUS

A. Introduction

LE is an autoimmune disease of unknown etiology affecting connective tissues and multiple organs. There are three major clinicopathological forms recognized. Systemic lupus erythematosus (SLE) is a chronic inflammatory disease involving multiple organs and a variety of cutaneous and oral manifestations. The clinical features vary tremendously, but the most common features are skin rashes, joint pain, fever, nephritis, and pleurisy. Chronic cutaneous lupus erythematosus (CCLE), or discoid lupus erythematosus, consists primarily of cutaneous and oral lesions. Although some patients with CCLE (<5%) may develop SLE, CCLE generally represents an independent entity with a good prognosis. A third form of LE, subacute cutaneous lupus erythematosus (SCLE) has clinical features of both SLE and CCLE, although systemic disease is usually mild. An overview of the clinicopathological features of these three forms of LE is presented.

B. Systemic Lupus Erythematosus

SLE is a disease that is five to ten times more likely to affect women than men and also more common in blacks (1:250) than whites (1:1000). The onset of symptoms most frequently occurs between the ages of 15 and 40 years, with the average age of 30 years; however, the disease can affect both the pediatric and older patient (1).

In the United States, the reported prevalence of SLE ranges from 14.6 to 50.8 cases per 100,000. The basic etiological event of SLE is unknown, although several factors have been proposed. Genetic factors include an increased incidence of clinical SLE or serological positivity in family members. In 40% of cases of neonatal SLE, the mothers will either demonstrate evidence of SLE, or will have developed SLE within a year after childbirth (2). The reported concordance rate of SLE in monozygotic twins is 25%. In 6% of SLE cases, patients have inherited deficiencies of early complement components, including C2 and C4 (2).

Circulating autoantibodies directed against nuclear material, also known as antinuclear antibodies (ANA), are the serological hallmark of SLE. From 95% to 100% of patients with SLE have positive ANA (3). Other autoantibodies to cytoplasmic material, blood proteins, and cell membranes are also present. These antibodies can have direct effect, with manifestations such as hemolytic anemia, thrombocytopenia, or leukopenia. Another major effect of these formed immune complexes, especially by nuclear antigens and ANA, is their deposition in blood vessel walls, glomerular basement membranes, and other sites. The complexes activate the complement system, with subsequent damage to the tissue sites.

Exogenous factors are also involved in the pathogenesis of SLE. Drugs, including procainamide, hydralazine, isoniazid, and quinidine, may cause drug-induced lupus, but this is limited to the duration of drug usage (4). One-third to two-thirds of patients with

SLE have photosensitivity, and ultraviolet light (UV) may precipitate or exacerbate the disease; however, the exact mechanism is unclear. Bacterial or latent viral infections have also been proposed as initiating events, although no clear evidence exists (1,4). Hormonal factors have long been considered in view of the high female incidence. Antiphospholipid antibodies associated with venous and arterial thrombosis are also seen.

The clinical features of SLE are varied, and because of this, a definitive diagnosis of SLE is often not made until a few years after the initial symptoms. Initial complaints include extreme fatigue, joint pain, and myalgia. Up to 85% of patients have mucocutaneous symptoms, including the classic butterfly rash over the malar region and bridge of nose in approximately 50% of patients (5). Oral mucosal lesions occur primarily on the palate, buccal mucosa, and gingivae. The clinical appearance can range from lichenoid to granulomatous, at times with ulceration. Alopecia, either diffuse or patchy may be encountered in SLE.

Renal involvement, referred to as lupus nephritis, can be seen in up to 50% of patients, although renal changes can be demonstrated in almost all cases of SLE when immunofluorescence and electron microscopy are used (6). The development of nephrotic syndrome and subsequent uremia is a serious complication of SLE and the most common cause of death. Cardiac involvement in the form of pericarditis is common. Nonbacterial verrucous endocarditis (Libman-Sacks endocarditis) can also be seen in 50% of the patients at autopsy, but is usually not clinically recognized. Central nervous systems symptoms can be noted with seizures and psychosis among the more serious neurological abnormalities.

C. Chronic Cutaneous Lupus Erythematosus

Patients with CCLE have limited disease, generally confined to mucocutaneous areas, and systemic involvement is rare. CCLE is also called discoid lupus erythematosus because the cutaneous lesions are characterized by well-defined, scaly, erythematous discoid patches. With time, many of the older lesions heal, with atrophic scarring. The cutaneous lesions most commonly affect the face, particularly the malar area and bridge of nose, although the scalp, ears, oral cavity, and the vermillion border of the lips can be affected. The oral lesions of CCLE may clinically resemble lichen planus (7). White, radiating striae surrounding an erythematous or ulcerated central zone typify the oral mucosal lesions (Fig. 15). At times, a more diffused nondescript erythematous patch can be seen, particularly on the palate (Fig. 16).

The exact pathogenesis of CCLE is unknown, but most likely involves genetic factors in the development of the disease. Exposure to UV light can trigger as well as exacerbate CCLE.

D. Subacute Cutaneous Lupus Erythematosus

In SCLE, widespread nonscarring cutaneous lesions arise mainly on the upper trunk and extensor part of

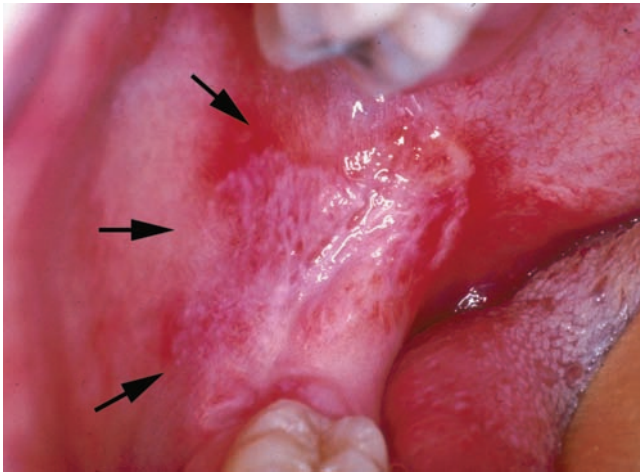


Figure 15 Chronic cutaneous lupus erythematosus presenting on the buccal mucosa as white radiating striae (arrows).



Figure 16 Nondescript erythematous patch on the palate from a patient with chronic cutaneous lupus erythematosus.

the arms. Although photosensitivity is present, the face is generally spared. Mild systemic disease, usually arthralgia, is present and renal disease is unusual.

E. Histopathology

The histopathological features of the oral lesions of the different forms of LE share similar characteristics (8,9). The epithelium can show either hyperorthokeratosis or hyperparakeratosis, with keratotic plugging (Fig. 17). Alternating areas of epithelial atrophy and acanthosis can be seen. At times, a lichenoid appearance is present, with sawtooth rete ridges. Basal cell liquefaction, colloid bodies or Civatte bodies, intraepithelial vesicles, and upward migration of lymphocytes can also be seen (Fig. 18). Subepithelial infiltration of lymphocytes can be seen both superficially and, more often, perivascularly, deep in the lamina propria. Many of these features are also present in oral lichen planus, with the exception of the deep perivascular infiltrate. One way to distinguish these two entities is by the presence

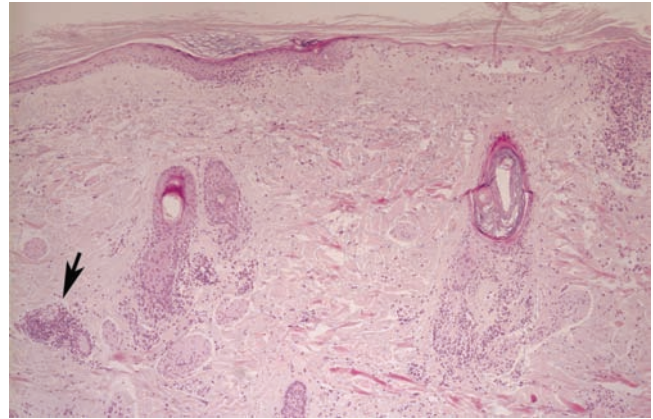


Figure 17 Chronic cutaneous lupus erythematosus. Epithelial atrophy, edema, and interface change is seen. A deep perivascular lymphocytic infiltrate is present (arrow).

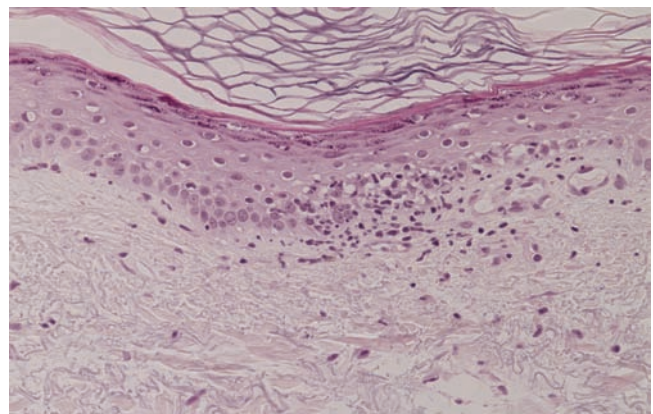


Figure 18 Higher magnification of Figure 17 showing hydropic degeneration of the basal cells and upward migration of lymphocytes.

in LE of continuous or patchy periodic acid-Schiff (PAS)-positive deposits juxtaepithelially (8,9).

The cutaneous lesions of LE are diagnosed by the presence of hyperkeratosis with keratotic plugging in the openings of hair follicles. Basal cell liquefaction and a patchy, predominately lymphocytic, infiltrate both around vessels and skin appendages are seen.

F. Diagnosis

The diagnosis of SLE includes both clinical and laboratory findings. The criteria for SLE proposed by the American College of Rheumatology (11) include the following:

1. Malar rash
2. Discoid rash
3. Photosensitivity

4. Oral ulcers
5. Nonerosive polyarthritis involving two or more peripheral joints
6. Serositis: pleuritis or pericarditis
7. Renal disorder: cellular casts, proteinuria greater than 500 mg/24 hr nephritic syndrome
8. Neurological symptoms: psychosis or seizures
9. Hematological abnormalities: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
10. ANA
11. Immunological disorder: anti-DNA or anti-SM antibodies.

The presence of any two abnormal immunological findings in addition to two clinical findings present serially or simultaneously constitutes a diagnosis of SLE. These autoantibodies are generally not present in CCLE, with less than 20% patients with a positive ANA. Most patients with SCLE will have a positive ANA.

Direct immunofluorescence of lesional tissue in patients with both SLE and CCLE shows a granular deposition of one or more immunoreactants (IgG, IgM, or C3) at the BMZ. The lupus band test uses direct immunofluorescence of normal uninvolved skin. The lupus band test is usually positive in patients with SLE, but not in patients with CCLE (12).

G. Treatment and Prognosis

The primary treatment of patients with SLE is preventive care with regular monitoring. Avoidance of sunlight is necessary to prevent exacerbation of disease. Nonsteroidal anti-inflammatory drugs can be used to treat minor manifestations or in combination with steroids to minimize steroid dose. High-dose steroid therapy should be limited, if possible, to four to six weeks, and maintenance therapy should be of the lowest dose possible, preferably alternate-day therapy. For acute episodes, immunosuppressive agents, including cyclophosphamide, chlorambucil, and azathioprine have been used, but are associated with significant toxic effects. Antimalarials, most commonly hydroxychloroquine, are effective for cutaneous, musculoskeletal, and mild systemic symptoms.

The treatment of CCLE is usually confined to topical corticosteroid administration to both the cutaneous and oral lesions. Those patients who fail to respond to corticosteroids may improve with systemic antimalarials. As with SLE, patients with CCLE should avoid exposure to sunlight.

The clinical course of SLE is highly variable; therefore, so is the prognosis. The disease is characterized by periods of flare-ups and remissions over a period of years and even decades. Over the years, prognosis has improved significantly. The five-year survival rate is 95% and then falls to 75% by 15 years. The most common causes of death are renal failure, intercurrent infections, and central nervous system complications (1,5–7).

The prognosis for patients with CCLE is quite good. For most patients, the lesions remain confined

to the skin and will eventually resolve in 50% of patients. However, development of SLE occurs in about 5% of patients with CCLE.

V. LICHEN PLANUS

A. Introduction

Lichen planus is a common, usually self-limiting eruption that affects mainly middle-aged adults and involves the skin, mucous membranes, hair, and nails. Approximately one-third of patients with oral lichen planus (OLP) and between 55% and 65% of patients with cutaneous lichen planus are women (1). Pediatric cases of lichen planus are most unusual, constituting only 2% to 3% of all patients (1).

B. Clinical Presentation

The cutaneous lesions of lichen planus consists of violaceous polygonal papules that tend to preferentially involve the flexural areas. A network of fine lace-like white lines, called Wickham's striae, can be observed in many of the papules. The skin lesions of lichen planus are pruritic, although 20% of affected patients are asymptomatic (2).

Next to cutaneous lesions, OLP is the most commonly reported form. In fact, 15% to 35% of patients have only oral manifestations of lichen planus (1). Three different forms or presentations of OLP have been described: reticular (papular, lacy, or plaque-like); erythematous (atrophic) and erosive (ulcerative or bullous) (3). The reticular form is most common; however, the erosive form is more commonly reported. This most likely because the erosive form may provoke a painful or burning sensation; hence, the patients seek treatment. The buccal mucosa is most commonly affected by the reticular form, although the lateral and dorsal tongue, the gingiva, and the palate may also be involved (Fig. 19) (4). The typical reticular pattern

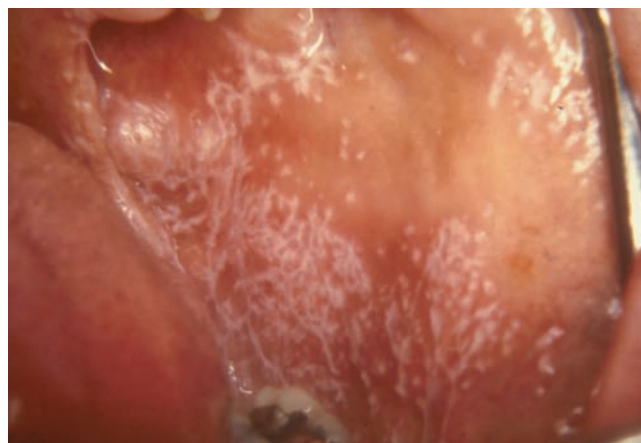


Figure 19 Lichen planus of the buccal mucosa exhibiting a white, reticulated lace-like pattern.



Figure 20 Lichen planus with typical plaque-like presentation on the dorsal tongue.



Figure 21 Erosive lichen planus of the buccal mucosa. Note the central ulceration surrounded by the white lace-like stria.

seen on the buccal mucosa is usually replaced by a more keratotic plaque when lichen planus occurs on the dorsal tongue (Fig. 20) (4).

Erosive lichen planus clinically shows varying degrees of erythematous areas with central ulcerations. On the periphery of these erosive areas, more typical Wickham's striae can be observed (Fig. 21). When the gingiva is involved, a picture of desquamative gingivitis may present, and biopsy specimens should be obtained to rule out other lesions that may present in a similar fashion (Fig. 22) (see discussion on MMP).

C. Lichenoid Drug Eruptions

Other entities can share both clinical and histopathological similarities to lichen planus. In some patients, oral mucosa in direct contact with dental amalgam can



Figure 22 Erosive lichen planus presenting as generalized desquamative gingivitis.

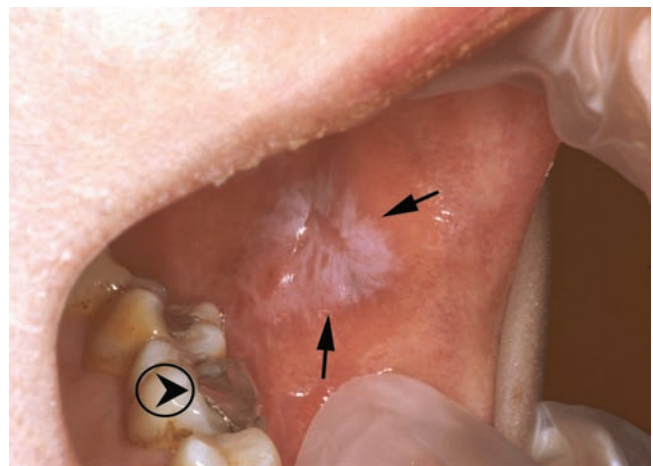


Figure 23 Lichenoid reaction to dental amalgam with lace-like reticulations (arrows). Note the large amalgam restoration which comes in direct contact with the affected mucosa (circled arrow).

produce a lichenoid reaction that mimics lichen planus (Fig. 23) (3,5). Biopsy material from these lesions is very similar to that seen in lichen planus; however, unlike lichen planus, these lesions resolve after removal of the adjacent amalgam filling.

Numerous drugs can produce a lichenoid mucosal reaction (Table 2) (1,5). Clinically, the lesions may present as either reticular or erosive or both. Unlike typical lichen planus, the lesions may be unilateral. The cause of lichenoid drug eruptions is unclear. Histology may help distinguish lichenoid lesions from classic lichen planus.

The use of cinnamon-flavored agents, including candy, chewing gum, mouthwash, toothpaste, and volatile oils, can result in an adverse mucosal reaction (6). The clinical presentation can vary, including

Table 2 Drugs Associated with Lichenoid Reactions

Antibiotics	Psychotropic
Ketoconazole	Lorazepam
<i>para</i> -Amino salicylic acid	Carbamezepine
Streptomycin	Nonsteroidal anti-inflammatory drugs
Tetracycline	Naproxen
Sulfonylureas	Indomethacin
Chlorpropamide	Diflunisal
Tolbutamide	Ibuprofen
Antimalarials	Fenclofenac
Chloroquine	Miscellaneous
Quinacrine	Arsenicals
Quinidine	Bismuth
Antihypertensives	Gold
Chlorothiazide	Mercury
Hydrochlorothiazide	Palladium
Methyldopa	Penicillamine
Propranolol	Allopurinol
Spironolactone	Mercaptopropionylglycine

Source: From Refs. 5, 7, 9; Sec. V (LICHEN PLANUS).



Figure 24 Lichenoid reaction to cinnamon-flavored chewing gum. This lesion resolved after gum chewing stopped.

erythema, ulceration, sloughing, and red and white lesions that clinically resemble lichen planus (Fig. 24).

Because the histopathology of these lichenoid lesions is similar to lichen planus, clinical correlation is imperative. Recent history of drug therapy or a new amalgam restoration may aid in arriving at the correct diagnosis. If symptomatic lichenoid reactions are a result of a drug reaction, then discontinuation or substitution of the medication is warranted.

D. Pathology

The histopathological features of OLP show varying degrees of orthokeratosis and parakeratosis. The epithelium may show atrophy or acanthosis, and often the rete ridges demonstrate a sawtooth pattern (Fig. 25). The BMZ figures prominently in the pathogenesis of lichen planus. The basal cell layer of the epithelium exhibits liquefaction (hydropic degeneration) (Fig. 26). Civatte bodies, which represent dyskeratotic basal ker-

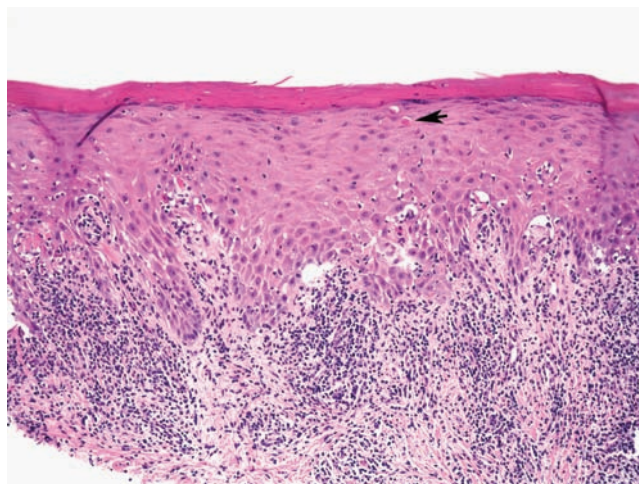


Figure 25 Lichen planus, oral mucosa. The lesion shows acanthosis, hyperparakeratosis, and sawtooth rete ridges. Occasional dyskeratotic cell is noted (arrow). A dense band-like lymphocytic infiltrate immediately subjacent to the epithelium is present.

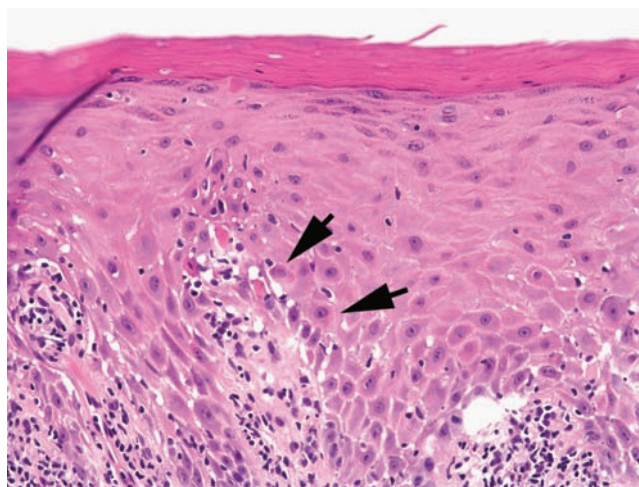


Figure 26 Lichen planus of the oral mucosa showing hydropic degeneration of basal cells. Civatte bodies are seen at the epithelium-connective tissue interface (arrows).

atinocytes that have undergone premature keratinization, can be seen at the epithelium-connective tissue interface. Another dominant feature is the band-like inflammatory infiltrate of predominately T lymphocytes that hug the basal layer. Cytological atypia should not be encountered in oral lichen planus; however, lesions superimposed with candidal infections may appear dysplastic. Biopsies of these lesions should be taken for re-evaluation after the candidal infection is treated. When dysplasia is noted, this should not be interpreted as lichen planus but rather as lichenoid dysplasia which is a potentially premalignant lesion.

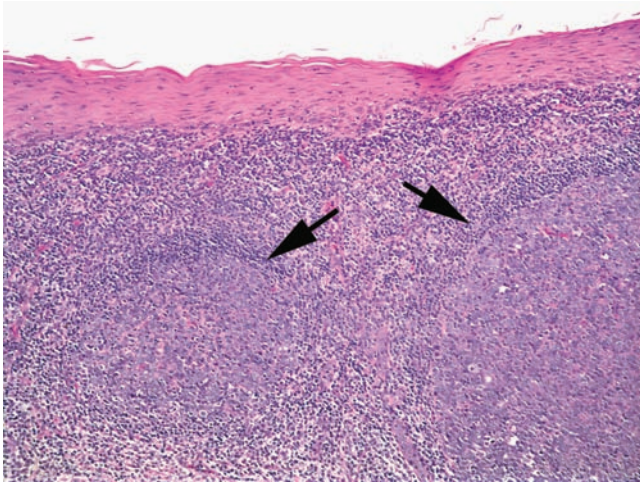


Figure 27 Lichenoid reaction to dental amalgam. Note the formation of lymphoid follicles within a dense lymphocytic infiltrate.

Although there are many microscopic similarities to lichen planus, lichenoid lesions have some notable differences. At times, the lymphocytic infiltrate is so dense that lymphoid follicles can be identified, which is particularly true in amalgam reactions (Fig. 27). Lichenoid drug reactions may have a more diffused lymphocytic infiltrate and contain eosinophils and plasma cells, and there may be more colloid bodies than in classic LP, but there are no specific features. The microscopic features of cinnamon-induced stomatitis share many of the features of lichen planus; however, the lichenoid band-like infiltrate contains a higher proportion of plasma cells than are expected in lichen planus. In addition, perivascular chronic inflammatory cell infiltrate is frequently seen (Fig. 28) (7).

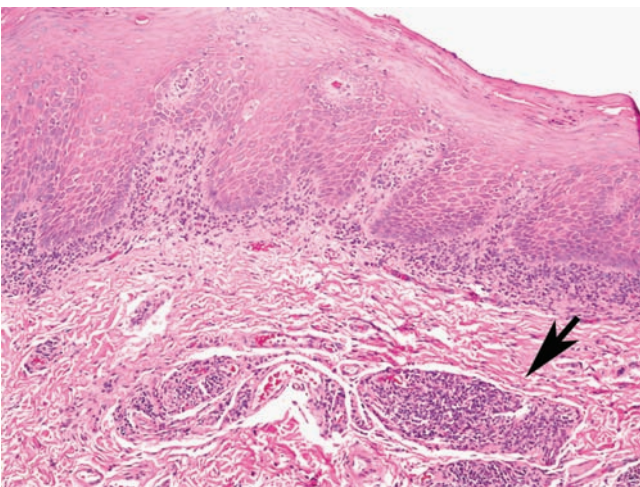


Figure 28 Lichenoid reaction to cinnamon. The lesion shares many similarities to lichen planus, although a perivascular chronic inflammatory cell infiltrate is frequently seen in cinnamon-induced stomatitis (arrow).

E. Immunopathology

The direct immunofluorescence pattern seen in lichen planus is not specific or diagnostic. Most lesions demonstrate the presence of fibrin or fibrinogen in a granular or linear pattern along the basement membrane (8). Although this finding is not diagnostic for lichen planus, it is useful in eliminating other vesiculo-ulcerative diseases. Occasionally, deposits of IgM, C3, IgG, and IgA are seen.

F. Immunology

The exact pathogenesis of lichen planus is unknown, although both antigen-specific and nonspecific mechanisms are proposed (9). The disease appears to represent a T cell-mediated immune response, and the majority of T cells within the epithelium and adjacent to the damaged basal cell are activated CD8 lymphocytes. In one hypothesis, intraepithelial, antigen-specific CD8 T cells trigger apoptosis of basal cell keratinocytes in OLP (9). Other research points to nonspecific events, including mast cell chemotaxis and degranulation, basement membrane disruption by matrix metalloproteinases, as well as T cells recruited by keratinocyte-derived chemokines.

G. Treatment and Prognosis

The treatment of OLP is dependent on disease extent. In patients with the reticular form of lichen planus, no therapy is required because this form rarely produces symptoms. At times, secondary candidiasis can cause a burning sensation, and antifungal therapy effectively relieves these symptoms. When patients present with limited oral erosive lichen planus, topical corticosteroids are recommended. For patients with extensive oral lesions, treatment with systemic corticosteroids, administered in tapering dosage; is effective.

Cyclosporine, dapsone, azathioprine, and psoralen and ultraviolet light A (PUVA) have also been used to treat symptomatic oral lesions of lichen planus; however, these reports are not controlled studies and include only a few patients (1). OLP is a chronic condition and can persist for up to 20 years (1,3). The erosive form is least likely to undergo spontaneous remission, whereas half of the reticular lesions will eventually resolve.

H. OLP and Malignant Potential

Controversy exists over the potential malignant transformation of OLP. Many reported cases of cancer arising in OLP were never documented histopathologically, or the histology demonstrated epithelial dysplasia. The malignant transformation cases that were reported occurred in patients with the atrophic, erosive pattern of OLP. Therefore, microscopic documentation of erosive, nonclassical forms of OLP as well as long-term clinical follow-up of patients with symptomatic OLP would be prudent.

VI. GRAFT-VERSUS-HOST DISEASE

Chronic graft-versus-host disease (GVHD) is a major cause of morbidity and mortality following allogeneic bone marrow transplantation (1). The median onset of chronic GVHD is six months posttransplantation. If symptoms appear within 100 days after bone marrow transplant, the condition is commonly referred to as acute GVHD. Primarily, the skin, liver, and gastrointestinal tract are involved in acute GVHD. This is in contrast with chronic GVHD that presents with a variable clinical picture, including dermal, ocular, hepatic, pulmonary, and gastrointestinal manifestations (1).

Oral complications of chronic GVHD can be seen in up to 80% of patients (1,2). Symptoms include xerostomia, with minor salivary glands that exhibit the histopathological features of Sjogren's syndrome. Oral lesions and infections are other common findings, and viral and fungal cultures are needed to institute appropriate therapy. Lichen planus-like lesions can appear as white, lacy, reticular striae, to more dense plaques on the buccal mucosa and tongue (Fig. 29).

Histological features of these lichenoid lesions show basal cell degeneration, intracellular edema of epithelial cells, dyskeratosis, and lymphocytic infiltration in the submucosa (Fig. 30). The lymphocytic infiltration is usually not as intense as seen in lichen planus, although a band-like lymphocytic infiltration can be seen. In addition, a few plasma cells and eosinophils can occasionally be seen. Immunologically, the lymphocyte population is composed of CD4 and CD8 T lymphocytes in the same ratio found in lichen planus (2,3). The diagnosis of GVHD is based on the clinical and histopathological findings because each patient may present with varied symptoms.



Figure 29 Graft-versus-host disease. Involvement of the tongue in a patient who underwent a bone marrow transplant for chronic myelogenous leukemia. Note the ulcerations that resemble erosive lichen planus.

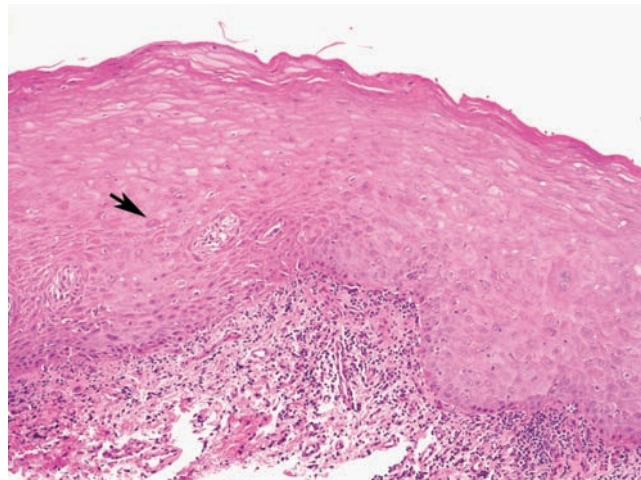


Figure 30 Graft-versus-host disease. Within the mucosa, groups of dyskeratotic keratinocytes can be seen (arrow). Hydropic degeneration of the basal cells overlying a moderate lymphocytic infiltrate is present.

VII. ERYTHEMA MULTIFORME

A. Introduction

Over 130 years ago, von Hebra first described EM as a disease of fever, malaise, and multiform lesions of the skin and mucous membranes. Stevens and Johnson in 1922 described a much more severe, acute febrile illness in two young boys, characterized by stomatitis, purulent conjunctivitis, and skin lesions similar to EM. There is some disagreement whether this mucocutaneous syndrome, subsequently called the Stevens-Johnson syndrome (SJS), represents a more severe variant of EM, also called EM major or represents a distinct disease (1).

In 1956, Lyell described a condition he termed toxic epidermal necrolysis (TEN), characterized by extensive detachment of full-thickness epidermis, partially or totally necrotic. Some patients with apparent SJS eventually developed detachment and sloughing of the epidermis, whereas other patients with TEN developed typical target lesions seen in EM. Some authors believe that TEN represents the most severe form of EM, whereas others prefer to recognize TEN as a distinct entity (2,3). The diagnostic criteria for EM, SJS, and TEN are listed in Table 3.

B. Clinical Presentation

EM minor typically develops in young adults (aged 20–40 years) and accounts for 80% of patients with EM (2,4). Skin lesions resembling a target or bull's eye are the hallmark of EM (Fig. 31). The skin lesions typically begin as flat, round, and dusky-red, then become slightly elevated. The most common sites are the extremities, with the dorsum of the hand a prevalent site. The cutaneous lesions are typically symmetrical

Table 3 Diagnostic Criteria for Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis**Erythema multiforme**

- Symmetrical involvement of the extremities
- Target (bull's eye) lesions
- Individual lesions <3 cm in diameter
- Mucous membrane involvement absent or confined to one site
- <20% of body surface area affected
- Biopsy specimen compatible with erythema multiforme

Stevens-Johnson syndrome

- Widespread involvement of the body surface
- Target lesions (typical or raised or flat atypical targets)
- Individual lesions <3 cm in diameter, poorly defined border, often confluent
- Extensive mucous membrane involvement of at least two sites
- <20% of body surface affected
- <10% of epidermal detachment

Toxic epidermal necrolysis

- Widespread involvement, prominent on trunk and proximal limbs
- Erythematous or purpuric macules, or flat, atypical target lesions
- Bullae

>30% of epidermal detachment

Mucosal erosions common, primarily oral and ocular mucosa

Source: From Refs. 2–4, 7; Sec. VII (ERYTHEMA MULTIFORME).

**Figure 31** Typical target or “bull’s eye” skin lesion characteristic of erythema multiforme.

and are generally a few centimeters or less in diameter (3). EM primarily involving the skin, with no more than one area of mucous membrane involvement, is usually termed EM minor. The lips are the most frequent site of oral involvement, followed by the buccal mucosa, labial mucosa, tongue, soft palate, and fauces (5). The oral lesions start as erythematous patches, which undergo necrosis, become ulcerated, and may hemorrhage. These oral lesions are quite painful, and dehydration may occur because of the inability of the patient to ingest liquids.

**Figure 32** Characteristic hemorrhagic crusting of the lips in a patient with erythema multiforme.

SJS represents approximately 20% of EM cases. Severe mucosal lesions develop in at least two mucosal sites—most commonly the oral mucosa and the eyes—although genitalia are also affected. The cutaneous lesions are similar to EM, although the eruptions are more often vesicular or bullous. These oral lesions are quite painful and are covered with a white or yellow exudate. When the gingiva is involved, a clinical picture of acute necrotizing ulcerative gingivitis (ANUG) is seen. The lip lesions show a characteristic hemorrhagic crusting (Fig. 32). In many cases of SJS, a prodromal period, consisting of an upper respiratory illness, with fever, cough, headache, and malaise, is noted before the onset. It is not entirely clear whether these symptoms are a primary manifestation of EM or are secondary to the disease that triggers EM. The mortality rate of SJS is reported to be between 0% and 10% (4).

The cutaneous lesions seen in TEN begin abruptly, with burning or painful eruptions located symmetrically on the face and chest, rapidly extending over the skin surface, prominently involving the trunk and proximal limbs (3). A positive Nikolsky sign (epidermal loss with lateral shearing), widespread, sheet-like loss of the epidermis, and oozing dermis are characteristic of TEN. Massive fluid loss through the denuded epidermis and bacterial colonization of the skin leading to systemic sepsis are major causes of mortality in TEN. Approximately 30% of patients with TEN die.

Mucosal involvement is present in 80% to 95% of cases of TEN, and in one-third of patients, it precedes cutaneous lesions by one to three days (3,4). The oral mucosa is most frequently involved, with extension into the pharynx. The eyes, genitalia, and anus may also be affected in TEN. Severe ocular involvements include corneal vesicles and acute iritis that can result in scarring of the lids and conjunctivae. The sequelae of ocular lesions are especially serious, affecting 30% to 40% of survivors, and early intervention is crucial.

C. Pathology

There is no specific histopathological picture for EM, reflective of the varied clinical presentations. Pronounced edema in the upper dermis can result in subepidermal blisters. A mixed inflammatory infiltrate, composed of lymphocytes, neutrophils, and occasionally, eosinophils, is present at times in a perivascular location and along the junction of the dermis and epidermis (Fig. 33). The inflammatory cells can migrate into the epidermis, and mild spongiosis and intracellular edema may result. Basal cells may show hydropic degeneration, and scattered throughout the epidermis, individually necrotic keratinocytes are seen (Fig. 34). These eosinophilic necrotic

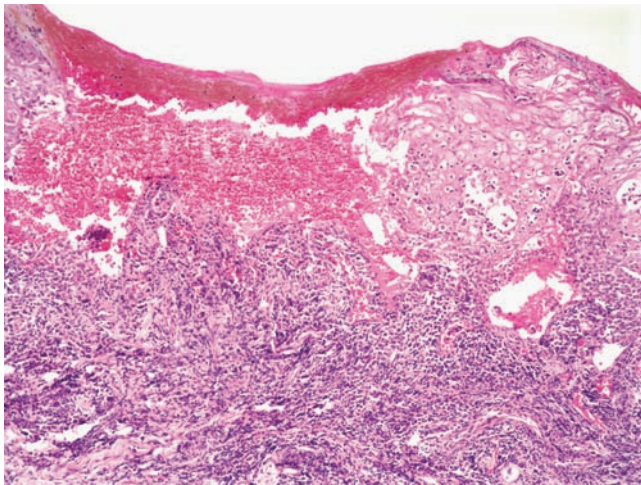


Figure 33 Erythema multiforme. Older lesion showing interface change with overlying necrotic keratinocytes. A mixed inflammatory infiltrate is seen in both the superficial and deep dermis.

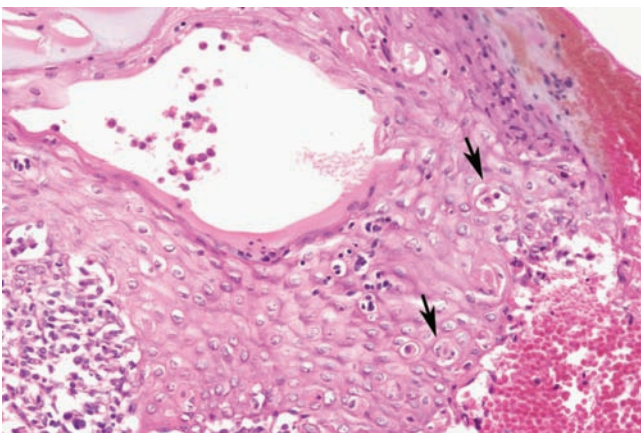


Figure 34 Erythema multiforme. The basal cells show hydropic degeneration and migrating into the epithelium are inflammatory cells. Multiple, individually necrotic keratinocytes can be seen (arrows).

keratinocytes are also called Civatte bodies or colloid bodies. Adjoining these necrotic keratinocytes are mononuclear cell infiltrates, an indication of satellite cell necrosis.

Deposits of IgM and C3 are found in the walls of blood vessels and along the BMZ on routine immunofluorescence examination (6). The finding of immune complexes on dermal vessels, although at one time was thought to denote immune complex vasculitis, is nonspecific.

D. Etiology

The etiopathogenesis of EM is obscure, although a wide range of factors have been suggested as triggering agents. Herpes simplex virus (HSV) infection type 1 and 2, with the subsequent development of EM, has been recognized for many years and accounts for over half of the cases of EM (6). Typically, a recurrent HSV lesion, usually herpes labialis, precedes EM by about 10 days. Of interest is that EM occurs after recurrent HSV infection, but not after a primary HSV infection. The clinical features of herpes-associated EM are consistent with a delayed-type hypersensitivity reaction. Helper T cells involved in cell-mediated immunity are recruited by keratinocytes and respond to viral antigens with production of interferon- λ initiating an inflammatory cascade.

Other agents implicated in the development of EM include *Mycoplasma pneumoniae*, drug reactions, mycotic infections, and less commonly, vaccinations, skin allergens, and protozoan infections. *Mycoplasma* infection, documented by both cultures and serology, is the most commonly recognized bacterial infection associated with EM (7). Because this infection is usually treated with antibiotics, it is often difficult to determine whether the antibiotic or the infection is the etiological factor.

Drug reactions cause the majority of SJS and TEN cases. Numerous drugs are associated with the onset of SJS and TEN, including the sulfonamides, anticonvulsants, nonsteroidal anti-inflammatory drugs, and antibiotics, such as amoxicillin and erythromycin (8). Drug-associated EM major and TEN may begin one to three weeks after drug initiation, although incidences where months have elapsed from the first dose of drug to the onset of symptoms have been documented.

E. Differential Diagnosis

The diagnosis of recurrent EM of the oral mucosa in the absence of cutaneous lesions may be difficult. Other mucocutaneous, ulcerative diseases, including aphthous ulcers, primary herpes, pemphigus, pemphigoid, and ANUG must be considered. Recurrent aphthous ulcers are generally restricted to nonkeratinized sites, whereas EM affects both keratinized and nonkeratinized tissue.

Primary herpetic stomatitis shares many of the clinical features of EM. However, primary herpetic stomatitis is not recurrent and usually involves the

gingiva, which is an unusual location for recurrent EM (5). Other vesiculoerosive diseases, including pemphigus and pemphigoid, occur in an older population, and immunofluorescence studies are diagnostic. When ocular involvement is present along with oral lesions, both Reiter's syndrome and Behçet's disease need to be ruled out.

F. Treatment and Prognosis

Treatment of EM varies with the severity of the outbreak. Usually, EM is treated symptomatically with analgesics and antipruritics. Antibiotics for lesions that become secondarily infected are also used. The use of systemic corticosteroids for EM is controversial (1,4). Some clinicians feel it reduces symptoms and slows the spread of eruption. However, extended use of these drugs may lower host resistance to HSV causing recurrent HSV and, subsequently, recurrent EM.

The use of acyclovir as a prophylactic agent in patients with a history of herpes-associated EM has been effective (4–6). This therapy is not effective in all patients, and reactivation of EM has occurred, even in the absence of a preceding HSV lesion.

Other treatments for severe outbreaks of EM have included cyclosporine, levamisole, thalidomide, dapsone, and cyclophosphamide. TEN is treated similarly to a major burn, with adequate antisepsis and fluid management.

VIII. RECURRENT APHTHOUS STOMATITIS

Recurrent aphthous stomatitis (RAS), also known as canker sores, are the most common oral ulcer estimated to affect up to 30% of adults and 37% of school-aged children (1). These painful ulcers generally last for 7 to 30 days and range in size from 1 mm to greater than 1 cm.

Generally, RAS is divided into three classes. Minor aphthous ulcers, the most common form, accounting for 80% of all aphthae, measure less than 1 cm and usually heal within 7 to 10 days. The minor aphthae may occur as a solitary lesion or in groups on movable, nonkeratinized tissue (Fig. 35). Major aphthae are characterized by large, deep ulcers larger than 1 cm in diameter. These painful lesions may take several weeks to heal, sometimes with submucosal scarring. Generally, major aphthae occur on the movable mucosa as well, particularly in the region of the soft palate and tonsillar fauces. The third type, herpetiform aphthae are small, about 1 or 2 mm in diameter, and usually occur as multiple ulcers, sometimes as many as 100 ulcers (Fig. 36). These ulcers can coalesce, and healing time is generally 7 to 10 days. Because of the small size and the large number of ulcers present, RAS can resemble primary HSV infection, however there is no association with herpes. A regional lymphadenitis may accompany an outbreak of any of these oral ulcers.

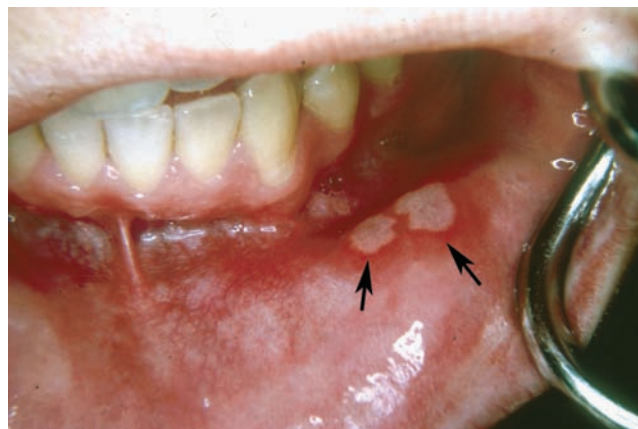


Figure 35 Minor recurrent aphthae on the lip (arrows). A white fibrinopurulent membrane is surrounded by erythema.



Figure 36 Herpetiform aphthous ulcerations present on the lip. Numerous small ulcers surrounded by erythema are seen.

A. Etiology

The search for the underlying cause of aphthous stomatitis has been investigated for many years (1,2). The etiology of RAS is thought to be multifactorial. Allergens have been reported to play an important role in triggering aphthae. Reported allergens include cinnamon, cereal products, tomatoes, nuts, chocolates, citrus as well as other fruits. Stress, anxiety, local mechanical trauma, nutritional deficiencies, and hormones are also reported to be associated with RAS. There are no known bacterial or viral infections associated with RAS, including HSV, *Helicobacter pylori*, and *Streptococcus*. Attempts to associate certain HLA types with aphthous stomatitis are not consistent, although a familial association has been observed in about 40% of cases.

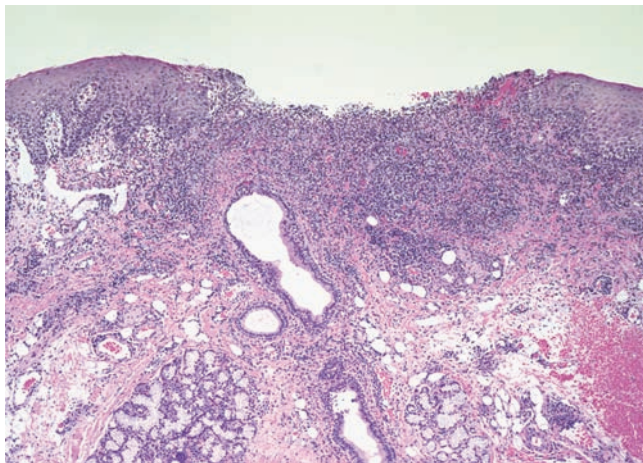


Figure 37 Recurrent aphthous ulcer of lip showing a central area of ulceration covered by a fibrinopurulent membrane. A mixed inflammatory cell infiltrate is seen in the lamina propria. This is essentially a nonspecific ulcer and diagnosis depends on clinical presentation.

B. Pathology

There are no diagnostic histological features of aphthous ulcers. Early lesions show a central area of ulceration covered by a fibrinopurulent membrane. The underlying lamina propria shows increased vascularity and a mixed inflammatory cell infiltrate, composed of lymphocytes, histiocytes, and neutrophils (Fig. 37). Definitive diagnosis is made from the clinical presentation and from exclusion of other diseases that mimic oral aphthae.

C. Immunopathology

The immunopathogenesis of RAS has become more defined in recent years with similarities to the pathogenic mechanisms seen in oral lichen planus. Increased numbers of activated cytotoxic T lymphocytes and natural killer (NK) cells are present in patients with active disease, whereas CD4 T lymphocytes are depressed (3). The cytotoxic T cells respond to a target antigen within the epithelium. The resultant lysis occurs, by the release of cytokines, including tumor necrosis factor. Similar to lichen planus, adhesion molecules probably regulate the movement of lymphocytes, although in RAS, the keratinocyte lysis occurs throughout the epithelium and not just at the basal cell layer, which is seen in lichen planus.

D. Differential Diagnosis

The oral ulcers seen in Behçet's disease clinically resemble RAS. In addition to oral ulceration, either genital or ocular lesions can occur. Usually, the oral ulcers are minor (i.e., smaller than 1 cm), however,

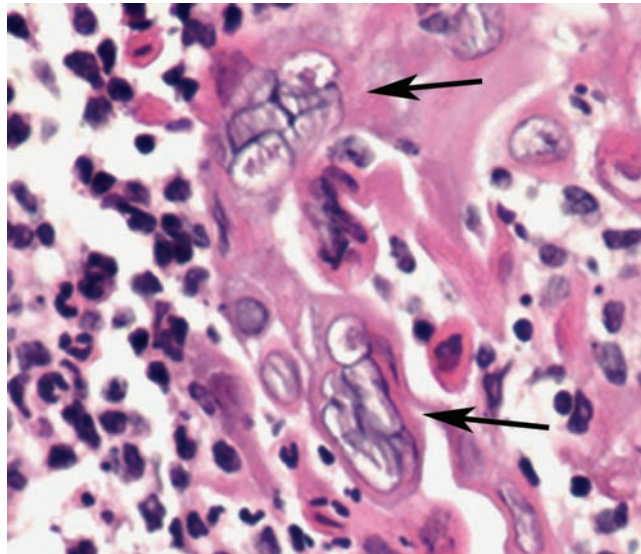


Figure 38 Herpes simplex virus. Cells exhibiting a viral cytopathic effect with multinucleated giant cells with condensation of the chromatin at the periphery (arrows).

major recurrent ulcers can be seen in the vulva or scrotum. Because the histopathological features of oral ulcers in Behçet's disease are nonspecific, the diagnosis remains clinical.

Intraoral herpes simplex virus type I (HSV I) can often be clinically mistaken for aphthous ulcers. However, both the etiology and the clinical location of these two types of ulcers are different. The most common location of recurrent HSV1 is the vermilion border of the lip (herpes labialis), also called a "fever blister" or "cold sore." However, recurrent HSV1 can also occur intraorally on keratinized tissue such as the hard palate and attached gingiva. Histological examination of an early HSV1-associated ulcer does show marked acantholytic epithelial cells termed "Tzanck cells." The infected cells show nuclear enlargement (ballooning degeneration) and condensation of the chromatin around the periphery of the nucleus (Fig. 38). The infected epithelial cells can fuse to form multinucleated cells. The adjacent mucosa is edematous with secondary inflammation. Older lesions may show nonspecific findings similar to RAS.

Another oral ulcer that may be clinically mistaken for RAS is traumatic ulcerative granuloma [traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), eosinophilic granuloma]. These ulcers most often occur on the lateral tongue or buccal mucosa adjacent to an identifiable source of irritation, such as a broken tooth (Fig. 39). Histologically traumatic ulcerative granulomas have a unique appearance. The granulation tissue extends into the deeper tissue including muscle and contains sheets of lymphocytes and histiocytes with scattered eosinophils (Figs. 40, 41). Often the epithelium exhibits hyperplasia.



Figure 39 Nonhealing ulcer on the lateral tongue. Biopsy proved to be a traumatic ulcerative granuloma.

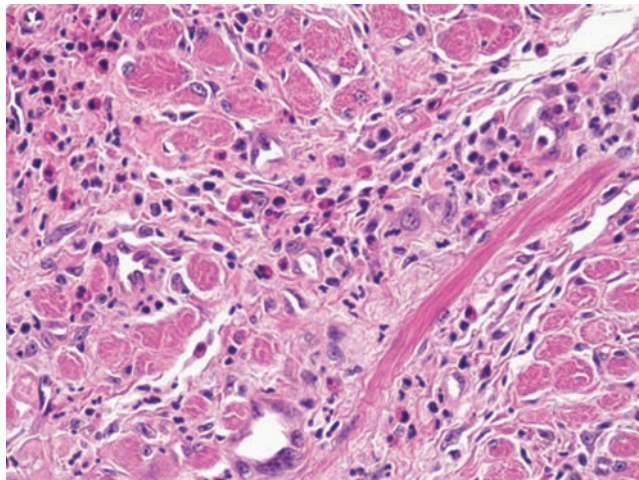


Figure 41 High power photomicrograph of Figure 40 demonstrating a mixed inflammatory cell infiltrate including eosinophils extending into the skeletal muscle.

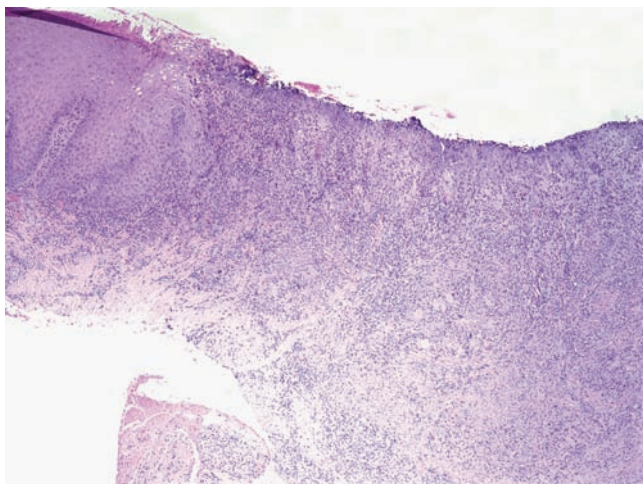


Figure 40 Traumatic ulcerative granuloma. Ulceration with a fibrinopurulent membrane. Inflammation extends deep into the underlying connective tissue.

E. Treatment and Prognosis

Because solitary aphthous ulcers are relatively asymptomatic and self-limiting, no therapy is required. Topical corticosteroids are usually effective in treating all three types of aphthae and produce the least number of side effects (1). When a patient presents with numerous ulcers and has had an unfavorable response to topical steroids in the past, then low-dose systemic corticosteroids can be used.

Other treatment modalities to manage RAS include chlorhexidine, topical and/or systemic

tetracycline, dapsone, and levamisole, but either conflicting results or questionable benefits compared with placebos exist (1,2,4). Cauterization and freezing agents should not be used to treat RAS, because further tissue damage ensues, with prolonged healing time.

Aphthae have a typical onset after puberty, and recurrences can occur sporadically for many years. As there is no cure for RAS, effective management is achieved with the foregoing agents.

REFERENCES

II. PEMPHIGUS

1. Becker BA, Gaspari AA. Pemphigus vulgaris and vegetans. *Dermatol Clin* 1993; 11:429–452.
2. Mutasim DF, Bilic M, Hawayek LH, et al. Immunobullous diseases. *J Am Acad Dermatol* 2005; 52:1029–1043.
3. Lamey PJ, Rees TD, Binnie WH, et al. Oral presentation of pemphigus vulgaris and its response to systemic steroid therapy. *Oral Surg Oral Med Oral Pathol* 1992; 74:54–57.
4. Mutasim DF, Adams BB. Immunofluorescence in dermatology. *J Am Acad Dermatol* 2001; 45:803–822.
5. Hashimoto T. Recent advances in the study of the pathophysiology of pemphigus. *Arch Dermatol Res* 2003; 295: S2–S11.
6. Virgili A, Thrombelli L, Calura G. Sudden vegetation of the mouth: pemphigus vegetans of the mouth (Hallopeau type). *Arch Dermatol* 1992; 128:398–402.
7. Iwata M, Watanabe S, Tamaki K. Pemphigus vegetans presenting as scrotal tongue. *J Dermatol* 1989; 16:159–160.
8. Fujimoto W, Hirano N, Miyashita M, et al. Pemphigus vegetans presenting with deafness, otalgia and facial nerve paralysis. *Br J Dermatol* 1991; 124:609–613.
9. Kaplan I, Hodak E, Ackerman L, et al. Neoplasm associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. *Oral Oncol* 2004; 40:553–562.

10. Anhalt GJ, Kim SC, Stanley JR, et al. Paraneoplastic pemphigus—an autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med* 1990; 323: 1729–1735.
11. Lam S, Stone MS, Goeken JA, et al. Paraneoplastic pemphigus, cicatricial conjunctivitis, and acanthosis nigricans with patchy dermatology in a patient with bronchogenic squamous cell carcinoma. *Ophthalmology* 1992; 99: 108–113.
12. Fullerton SH, Woodley DT, Smoller BR, et al. Paraneoplastic pemphigus with autoantibody deposition in bronchial epithelium after autologous bone marrow transplantation. *JAMA* 1992; 267:155–1502.
13. Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. *Arch Dermatol* 1992; 128:1091–1095.
14. Su WP, Oursler JR, Muller SA. Paraneoplastic pemphigus: a case with high titer of circulating anti-basement membrane zone autoantibodies. *J Am Acad Dermatol* 1994; 30:841–844.
15. Camisa C, Helms TN. Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. *Arch Dermatol* 1993; 129:883–886.
16. Brenner S, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. *Clin Dermatol* 1998; 16:393–397.
17. Sami N, Yeh SW, Ahmed AR. Blistering diseases in the elderly: diagnosis and treatment. *Dermatol Clin* 2004; 22:73–86.
3. Gill JM, Quisel AM, Rocca PV, et al. Diagnosis of systemic lupus erythematosus. *Am Fam Physician* 2003; 68: 2179–2186.
4. Hess EV, Farhey Y. Epidemiology, genetics, etiology and environmental relationships of systemic lupus erythematosus. *Curr Opin Rheumatol* 1994; 6:474–480.
5. Lahita RG. Overview of lupus erythematosus. *Clin Dermatol* 1993; 10:389–392.
6. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. *Medicine* 1993; 72:113–124.
7. Burge SM, Frith PA, Juniper RP, et al. Mucosal involvement in systemic and chronic cutaneous lupus erythematosus. *Br J Dermatol* 1989; 121:727–741.
8. Schiodt M. Oral discoid lupus erythematosus. III. A histopathologic study of sixty-six patients. *Oral Surg Oral Med Oral Pathol* 1984; 57:281–293.
9. Karjalainen TK, Tomich CE. A histopathologic study of oral mucosal lupus erythematosus. *Oral Surg Oral Med Oral Pathol* 1989; 67:547–559.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725, (letter).
11. David-Bajar KM, Bennion SD, DeSpain JD, et al. Clinical, histologic, and immunofluorescent distinctions between subacute cutaneous lupus erythematosus and discoid lupus erythematosus. *J Invest Dermatol* 1992; 99:251–257.

III. PEMPHIGOID

1. Korman NJ. Bullous pemphigoid. *Dermatol Clin* 1993; 11:483–498.
2. Laskaris G, Sklavounou A, Stratigos J. Bullous pemphigoid, mucous membrane pemphigoid and pemphigus vulgaris. *Oral Surg Oral Med Oral Pathol* 1982; 54: 656–662.
3. Mutasim DF, Adams BB. Immunofluorescence in dermatology. *J Am Acad Dermatol* 2001; 45:803–822.
4. Yancy KB. The pathophysiology of autoimmune blistering diseases. *J Clin Invest* 2005; 115:825–828.
5. Sami N, Yeh SW, Ahmed AR. Blistering diseases in the elderly: diagnosis and treatment. *Dermatol Clin* 2004; 22:73–86.
6. Chan LS, Ahmed R, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid. *Arch Dermatol* 2002; 138:370–379.
7. Higgins GT, Allan RB, Hall R. Development of ocular disease in patients with mucous membrane pemphigoid involving the oral mucosa. *Br J Ophthalmol* 2006; 90: 964–967.
8. Mutasim DF, Pelc NJ, Anhalt GJ. Cicatricial pemphigoid. *Dermatol Clin* 1993; 11:499–510.
9. Sollecito TP, Parisi E. Mucous membrane pemphigoid. *Dent Clin N Am* 2005; 49:91–106.
10. Hallel-Halevy D, Nadelman C, Chen M, et al. Epidermolysis bullosa acquisita: update and review. *Clin Dermatol* 2001; 19:712–718.

IV. LUPUS ERYTHEMATOSUS

1. Michet CJ Jr., McKenna CH, Elveback LR, et al. Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc* 1985; 60:105–113.
2. Deapen D, Escalante A, Weinrib L, et al. A revised estimate of twin concordance in systemic lupus erythematosus. *Arthritis Rheum* 1992; 35:311–319.

V. LICHEN PLANUS

1. Boyd AS, Neldner KH. Lichen planus. *J Am Acad Dermatol* 1991; 25:593–618.
2. Felner MJ. Lichen planus. *Int J Dermatol* 1980; 19:71–75.
3. Eisen D. The clinical manifestations and treatment of oral lichen planus. *Dermatol Clin* 2003; 21:79–89.
4. Silverman S, Gorsky M, Lozada-Nur F. A prospective follow-up study of 570 patients with oral lichen planus: persistence, remission, and malignant association. *Oral Surg Oral Med Oral Pathol* 1985; 60:30–34.
5. Jankittivong A, Langlais RP. Allergic stomatitis. *Semin Dermatol* 1994; 13:91–101.
6. Miller RL, Gould AR, Bernstein ML. Cinnamon-induced stomatitis venenata. *Oral Surg Oral Med Oral Pathol* 1992; 73:708–716.
7. DeRossi SS, Ciarrocca KN. Lichen planus, lichenoid drug reactions, and lichenoid mucositis. *Dent Clin North Am* 2005; 49:77–89.
8. Fith NA, Rich AM, Radden BG, et al. Assessment of the value of immunofluorescence microscopy in the diagnosis of oral mucosal lichen planus. *J Oral Pathol Med* 1990; 19:295–297.
9. Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med* 2002; 13:350–365.

VI. GRAFT-VERSUS-HOST DISEASE

1. Nakamura S, Hiroki A, Shinohara M, et al. Oral involvement in chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 82:556–563.
2. Soares AB, Faria PR, Magna LA, et al. Chronic GVHD in minor salivary glands and oral mucosa: histopathological and immunohistochemical evaluation of 25 patients. *J Oral Pathol Med* 2005; 34:368–373.

3. Mattisson T, Sundqvist KG, Heimdahl A, et al. A comparative immunological analysis of the oral mucosa in chronic graft-versus-host disease and oral lichen planus. *Arch Oral Biol* 1992; 37:538–547.

VII. ERYTHEMA MULTIFORME

1. Assier H, Bastufi-Garin S, Revuz J, et al. Erythema multiforme with mucous membrane involvement with Stevens-Johnson syndrome are clinically different disorders with different causes. *Arch Dermatol* 1995; 131:539–543.
2. Léauté-Labrèze C, Lamireau T, Chawki D, et al. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child* 2000; 83:347–352.
3. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol* 2007; 56:181–200.
4. Ayangco L, Rogers RS. Oral manifestations of erythema multiforme. *Dermatol Clin* 2003; 21:195–205.
5. Farthing PM, Maragou P, Coates M, et al. Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme. *J Oral Pathol Med* 1995; 24:9–13.

6. Huff JC. Erythema multiforme and latent herpes simple infection. *Semin Dermatol* 1992; 11:207–210.
7. Lamoreux MR, Sternbach MR, Hsu WT. Erythema multiforme. *Am Fam Physician* 2006; 74:1883–1888.
8. McKenna JK, Leiferman KM. Dermatologic drug reactions. *Immunol Allergy Clin N Am* 2004; 24:399–423.

VIII. RECURRENT APHTHOUS STOMATITIS

1. Zunt SL. Recurrent aphthous stomatitis. *Dermatol Clin* 2003; 21:33–39.
2. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis—a consensus approach. *J Am Dent Assoc* 2003; 134:200–207.
3. Eversole LR. Immunopathology of oral mucosal ulcerative, desquamative, and bullous diseases. *Oral Surg Oral Med Oral Pathol* 1994; 77:555–571.
4. Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol* 2005; 52:500–508.

Premalignant Lesions of the Oral Cavity

Pieter J. Slootweg

Department of Pathology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Thijs A.W. Merks

Department of Oral and Maxillofacial Surgery, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

I. DEFINITION

Premalignant lesions of the oral cavity are conditions of the epithelial part of the oral mucosal lining that carry an increased risk for the development of oral squamous cell carcinoma (OSCC) in that area. This group encompasses a mixture of lesions that are defined by clinical appearance, histology, or etiology (Table 1) (1). For some of these lesions, the premalignant character is doubtful as will be elaborated when discussing them. Moreover, it should be realized that lesions may not only be premalignant in the sense defined above but could also be risk factors, indicating an increased risk for developing OSCC anywhere in the upper aerodigestive tract (2,3). Moreover, other lesions could indicate an increased risk for the development of OSCC without being premalignant themselves.

Before going into detail about the various entities, histological items emanating when discussing mucosal premalignancies will be addressed.

II. DYSPLASIA

“Dysplasia” is the term that is used within the context of mucosal premalignancies. For the sake of clarity, one has to distinguish between cellular changes and architectural changes. The combination of both leads to a diagnosis that is communicated to the clinician with the aim to have a guide in management of the individual patient. This aim however is only poorly attained in a lot of instances, either because of lack of adequate and reproducible histological criteria or because of poor correlations between dysplasia and risk for malignant degeneration (1).

A. Cellular Alterations in Dysplasia

When assessing epithelial dysplasia, one should evaluate the presence of alterations of individual epithelial cells (4). Cells show dark-staining nuclei, an increased nuclear-to-cytoplasmic ratio, as well as variation in

size and shape. In addition, the nuclei also show marked variation in size and may have enlarged nucleoli. An increase in mitotic activity can also be seen in many reactive lesions but abnormal mitoses as well as mitotic figures found in unusual locations above the basal cell layer indicate premalignant cellular alterations. Individually keratinized cells or concentric rings of flattened keratinocytes below the surface layer also distinguish epithelial dysplasia from hyperplasia (Fig. 1A, B).

B. Tissue (Architectural) Alterations in Dysplasia

Tissue alterations in dysplasia can be summarized as loss of the orderly cellular maturation from basal cells to flattened superficial cells that may keratinize or not, depending on the site in the oral cavity (Fig. 2). Thickening of one of these epithelial layers without disturbance of this orderly layered architecture should not be interpreted as dysplastic (Fig. 3A, B). A grading system for dysplastic oral epithelium must take into consideration both the degrees of cellular atypia, in addition to the extent of structural tissue alterations as described above.

III. CLASSIFICATION/GRADING OF INTRAEPITHELIAL ALTERATIONS

In spite of shortcomings such as inter- and intraobserver variability and absence of clear-cut prognostic significance, traditional light microscopic examination still remains the most reliable method for determining the grade of intraepithelial alterations summarized under the designation dysplasia. Possibly because of these above-mentioned problems, competing classification systems exist and therefore there are no worldwide generally accepted criteria for a histological grading system in the head and neck region. As a result of this lack of unanimity, three schemes are currently used, which will be discussed in more detail. They are the

Table 1 Potentially Malignant Lesions of the Oral Mucosa

Disease name	Malignant transformation potential
Proliferative verrucous leukoplakia	*****
Erythroplakia	*****
Nicotine palatinus in reverse smokers ^a	*****
Oral submucous fibrosis	****
Speckled, granular (nonhomogeneous) leukoplakia	****
Actinic cheilitis	***
Smooth, thick (homogeneous) leukoplakia	**
Smokeless tobacco keratosis	*
Lichen planus	*

^aReverse smoking: smoking with the lit end of the cigarette in one's mouth.
Source: From Ref. 1.

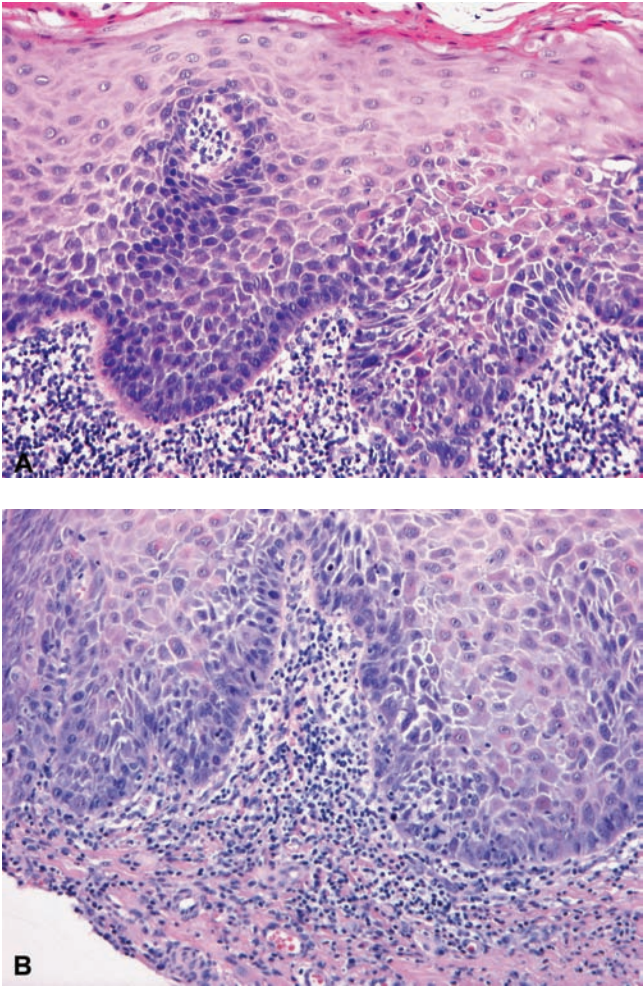


Figure 1 Photomicrograph to show cytonuclear atypia, both due to nuclear atypia as well as to increased cytoplasmic eosinophilia, indicating premature keratinization. (A) Low power view. (B) Higher magnification.

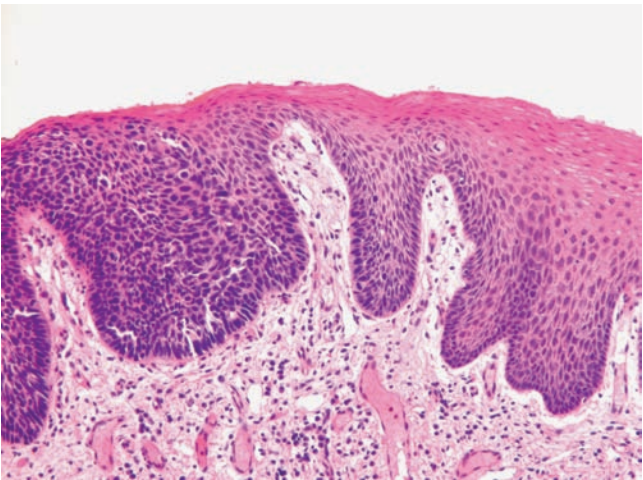


Figure 2 Disordered maturation indicating dysplasia may alternate with hyperplastic epithelial areas.

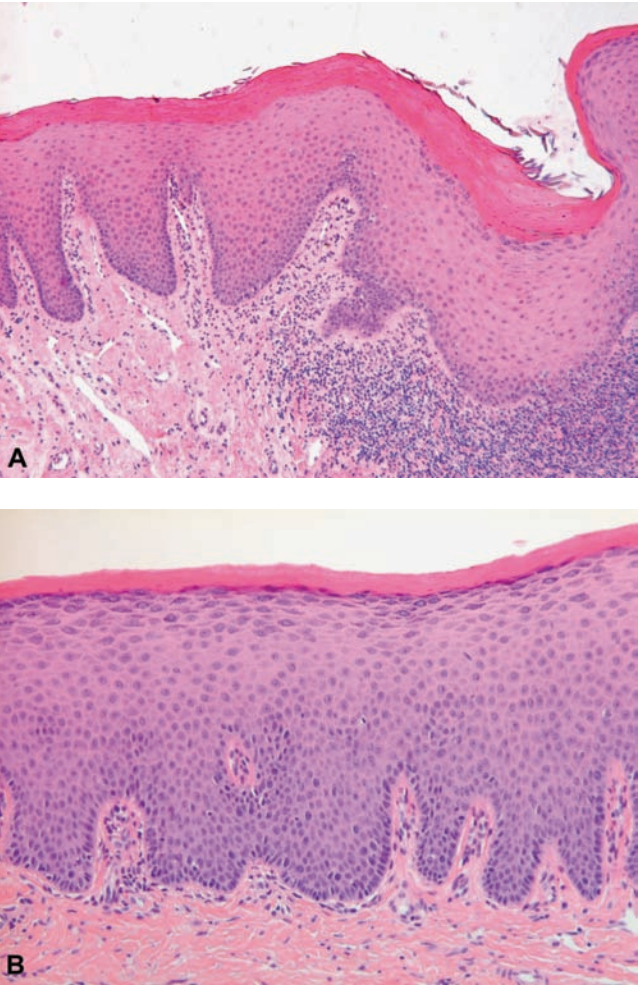


Figure 3 Hyperkeratosis may occur (A) with epithelial hyperplasia as well as (B) without epithelial hyperplasia.

World Health Organization (WHO) dysplasia criteria for classifying intraepithelial alterations in the oral cavity and larynx, the squamous intraepithelial neoplasia system, and the Ljubljana classification, the latter initially devised not only for the interpretation of laryngeal lesions but also being thought to be applicable for lesions in the oral cavity (4–7).

A. WHO Dysplasia Classification

The WHO dysplasia system includes the following categories.

Hyperplasia with Increased Number of Cells

There may be an increased number of cells in the spinous layer (acanthosis) (Fig. 3) or in the basal and parabasal cell layers (basal cell hyperplasia). The architecture of epithelium is preserved; there is no cellular atypia.

Dysplasia with Three Grades

Mild Dysplasia Architectural disturbance is limited to the lower third of the epithelium and is accompanied by cytological atypia (Fig. 4).

Moderate Dysplasia Architectural disturbance that extends into the middle third of the epithelium is the initial criterion for recognizing this category of dysplasia (Fig. 5A, B). However, consideration of the degree of cytological atypia may require upgrading to severe dysplasia.

Severe Dysplasia Architectural disturbance with associated cytological atypia is greater than two-thirds

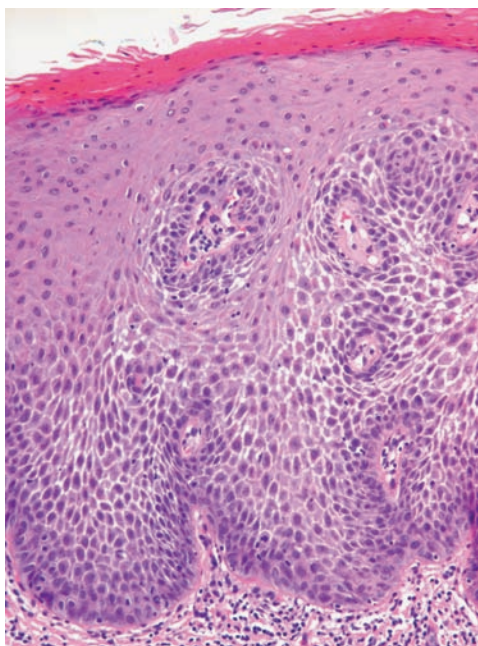


Figure 4 Photomicrograph showing mild dysplasia, epithelial alterations being confined to the lower third of the epithelial thickness.

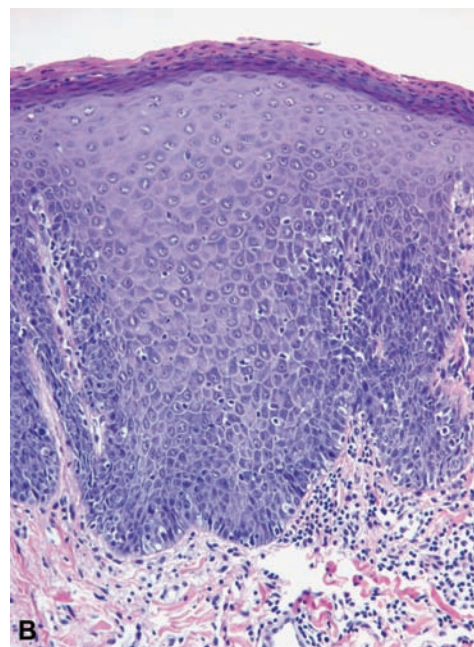
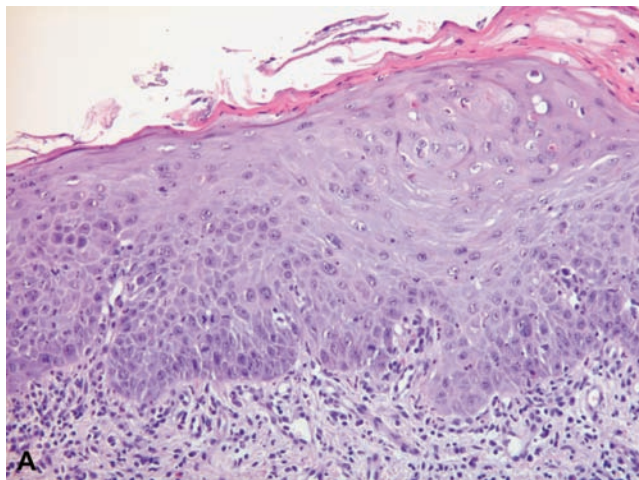


Figure 5 In moderate dysplasia, the epithelial alterations extend into the upper part of the epithelial thickness. They may occur (A) without an increase in the epithelial width or (B) with an increase in the epithelial width.

of the epithelium (Figs. 6A, B, C). However, as noted when discussing moderate dysplasia, architectural disturbance limited to the lower and middle third of the epithelium but with sufficient cytological atypia may be included in this category.

Carcinoma In Situ

Carcinoma in situ is represented by full or almost full thickness architectural abnormalities in the viable cellular layers accompanied by pronounced cytological atypia (Fig. 7A, B). Atypical mitotic figures and abnormal superficial mitoses are commonly present.

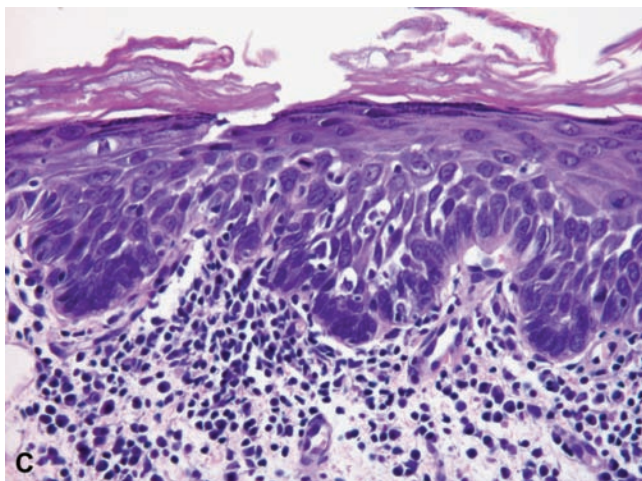
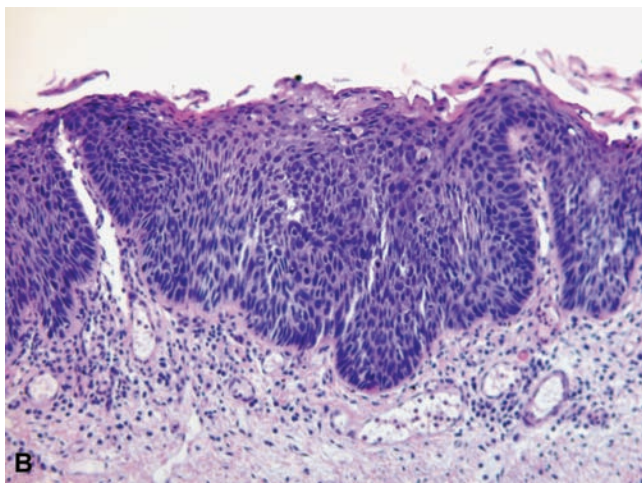
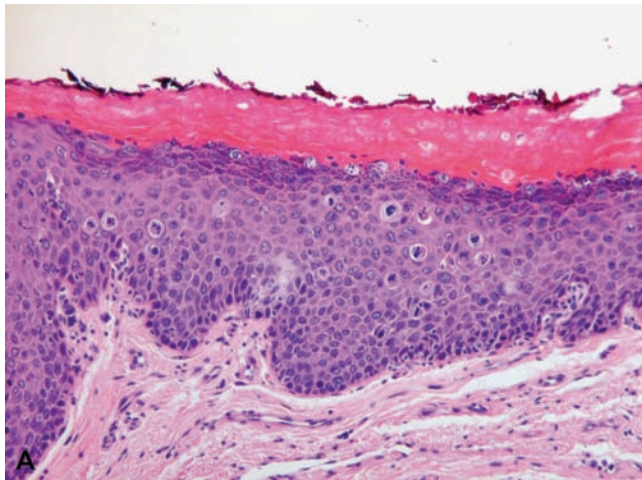


Figure 6 In severe dysplasia, atypical cells are dispersed throughout the entire epithelial thickness. This may occur together (A) with hyperkeratosis, (B) with an increase of epithelial thickness, or even (C) with thinning of the epithelium.

Although the architectural alterations for the various WHO stages are clearly defined, a lack of consensus on the extent of cytological atypia necessitating an

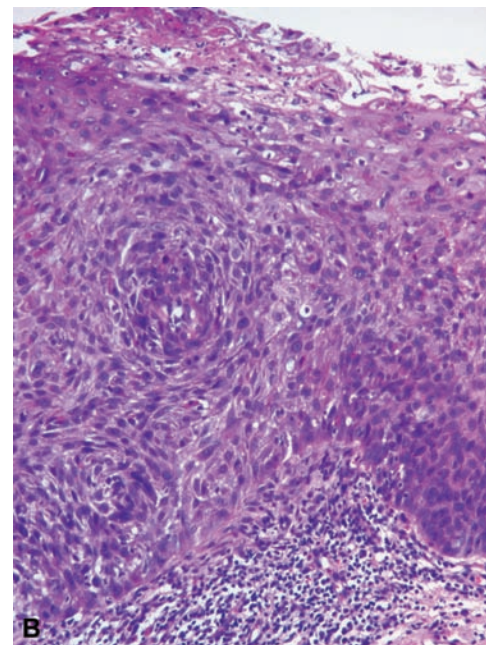
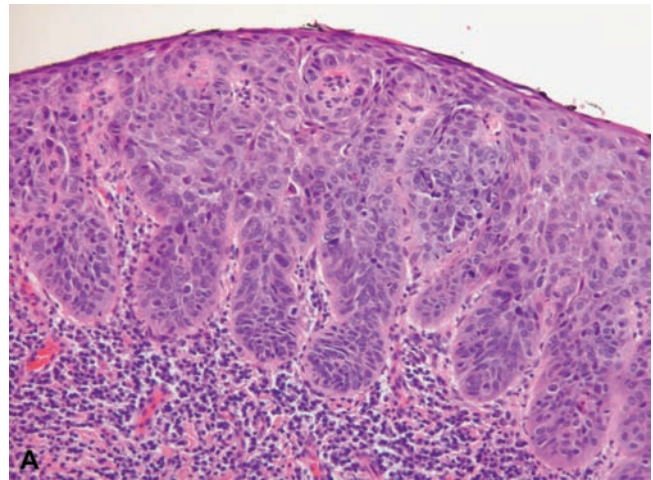


Figure 7 In in situ cancer, not only the whole epithelial thickness is involved but also the epithelial flattening at the surface is rudimentary or absent. In (A), there are also bulb-shaped rete ridges, and in (B), there is intercellular edema in the upper part of the epithelial covering.

upgrade from moderate-to-severe dysplasia makes this latter criterion rather equivocal, thus the drawing of a distinct line between both categories, making a subject of debate in individual cases.

B. Squamous Intraepithelial Neoplasia Classification

In this classification scheme, oral intraepithelial neoplasia grade 1, 2, and 3 are synonymous with the categories mild dysplasia, moderate dysplasia, and severe dysplasia as defined in the WHO. The most severe intraepithelial alterations are called carcinoma in situ in both classifications (4).

C. Ljubljana Classification

Within the Ljubljana grading system, the following categories are distinguished (4,5).

Reactive Lesions Having a Minimal Risk of Progression to Invasive Carcinoma

Squamous (Simple) Hyperplasia This is a benign hyperplastic process with retention of the normal architectural and cytological pattern of the squamous epithelium. The epithelium is thickened as a result of an increased prickle cell layer. The cells of the basal and parabasal region, which comprise one to three layers, remain unchanged. There is no cellular atypia; infrequent, regular mitoses are seen in the basal layer (Fig. 8).

Basal and Parabasal Cell Hyperplasia (Abnormal Hyperplasia) This can be defined as a benign augmentation of basal and parabasal cells in the lower part of the epithelial layer, while the upper part, containing regular prickle cells, remains unchanged. The thickened epithelium consists of an increased number of basal and parabasal cells without significant nuclear changes and occupying up to one-half or occasionally slightly more of the entire epithelium (Fig. 9). Rare, regular mitoses may be seen, always located in or near the basal layer. Less than 5% of epithelial cells show dyskeratosis, a premature and abnormal keratinization of individual cells or groups of cells that have no prickles and strongly eosinophilic cytoplasm.

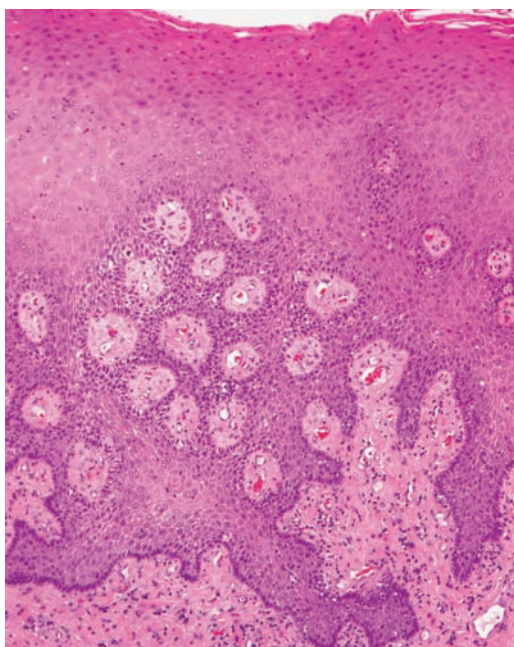


Figure 8 Photomicrograph showing squamous (simple) hyperplasia as defined in the Ljubljana classification. It concerns a benign hyperplastic process with retention of the normal architectural and cytological pattern of the squamous epithelium. The epithelium is thickened as a result of an increased prickle cell layer. *Source:* Picture courtesy of Prof. N. Gale, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

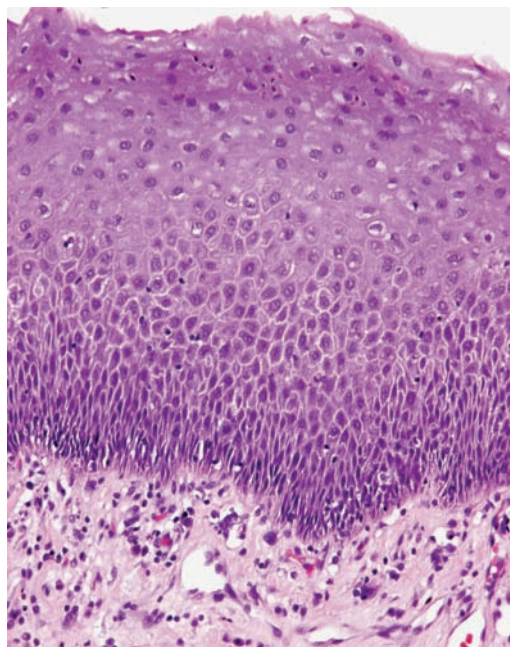


Figure 9 Photomicrograph showing abnormal hyperplasia as defined in the Ljubljana classification. The thickened epithelium consists of an increased number of basal and parabasal cells without significant nuclear changes and occupying up to one-half or occasionally slightly more of the entire epithelium. *Source:* Picture courtesy of Prof. N. Gale, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

Potentially Malignant Lesions

Atypical Hyperplasia (Risky Epithelium) This is a lesion with a definitely increased risk of progressing to invasive carcinoma that is characterized by the following histological appearances.

Stratification is still preserved in the epithelium. There is an increased number of epithelial cells with atypical features that may occupy the lower half or more of the entire epithelial thickness. Mitoses are moderately increased. They are usually found in the lower two-thirds of the epithelium, although they may occasionally appear at a higher level (Figs. 10, 11). Mitoses are rarely, if ever, abnormal. Dyskeratotic cells are frequent within the entire epithelium. Two subdivisions of atypical hyperplasia are recognised: (i) the more frequent “basal cell type” with no intercellular prickles and no cytoplasmic eosinophilia and the cells aligned perpendicularly or at an acute angle to the basement membrane and (ii) the less frequent “spinous cell type” [analogous to so-called “keratinizing dysplasia,” as defined by Crissman and Zarbo (8)] with intercellular prickles and increased cytoplasmic eosinophilia.

Actually Malignant Lesions

This group comprises carcinoma in situ, a lesion showing the features of carcinoma without invasion. There is loss of stratification or maturation of the

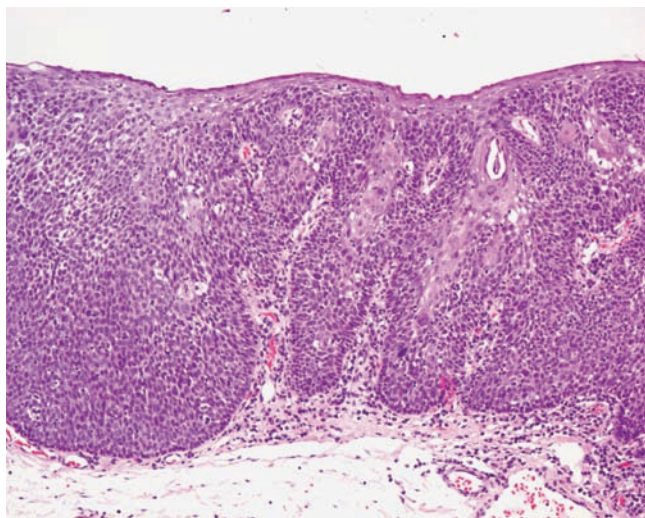


Figure 10 In atypical hyperplasia, according to the Ljubljana classification, an increased number of epithelial cells with atypical features may occupy the lower half, or more of the entire epithelial thickness. Mitoses are moderately increased. They are usually found in the lower two-thirds of the epithelium, although they may occasionally appear at a higher level. *Source:* Picture courtesy of Prof. N. Gale, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

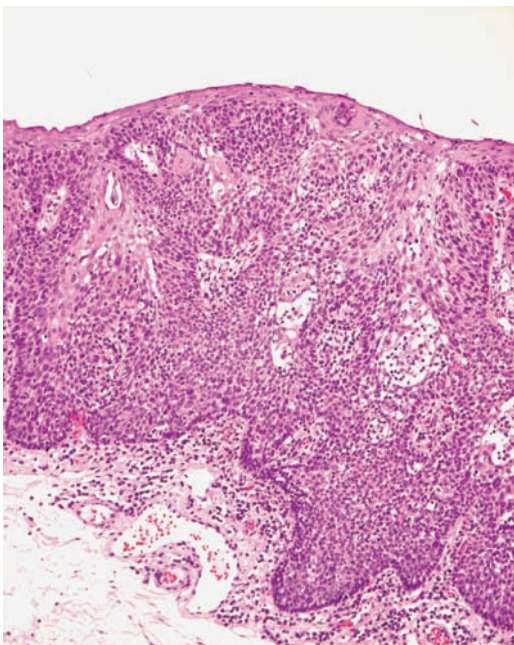


Figure 11 Another example of atypical hyperplasia, as defined in the Ljubljana classification. Atypical cells occupy the major part of the epithelium. In the WHO classification, such a picture would qualify as severe dysplasia or carcinoma in situ. *Abbreviation:* WHO, World Health Organization. *Source:* Picture courtesy of Prof. N. Gale, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

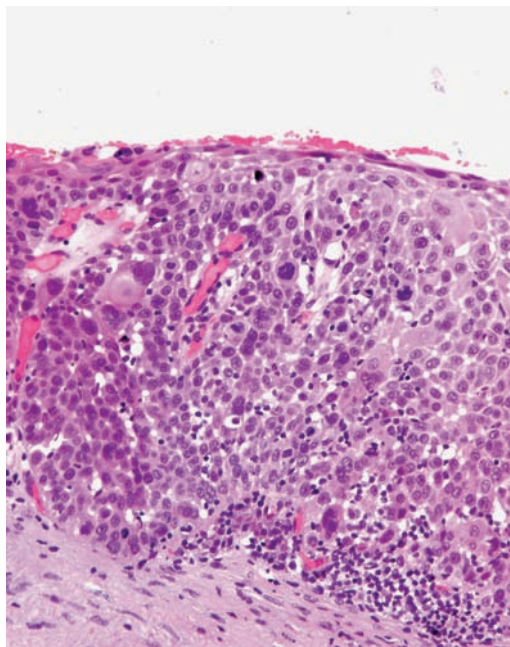


Figure 12 Photomicrograph showing carcinoma in situ. On this topic, there are no discrepancies between the WHO and the Ljubljana classification. *Abbreviation:* WHO, World Health Organization. *Source:* Picture courtesy of Prof. N. Gale, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

epithelium as a whole, although at the surface of the epithelium compressed, horizontally stratified, and sometimes keratinized cells may occur. Moreover, epithelial cells may show all the cytological characteristics of invasive squamous cell carcinoma, and mitotic figures are usually markedly increased throughout the whole epithelium, often more than five in one high-power field (Fig. 12). Abnormal mitoses are also frequently seen.

IV. CORRELATION BETWEEN DYSPLASIA GRADES AND MALIGNANT TRANSFORMATION

The association between dysplastic alterations in the oral mucosal lining and the subsequent development of OSCC has been known since long. In fact, the existence of such an association is the only point that can be stated firmly, other more precise data on this issue widely diverging or lacking.

The time span between diagnosing the presence of a cancer developing from a dysplastic lesion usually lasts two to five years from the moment the dysplasia is diagnosed, but may also be much longer (1,9,10). Malignant transformation rates for oral carcinoma in situ or combined carcinomas in situ and severe dysplasia varies between 7% and 50% (1). So, there appears to be a long period of time during which

malignant transformation may occur, and figures about the risk of malignant transformation of even the lesions with the more severe intraepithelial alterations diverge widely. This wide range of data on time evolving before malignancy occurs and on risk of malignant degeneration may be related to different patient populations and gaps in our knowledge concerning the relationship between premalignant mucosal changes and risk for development of malignancy. It might also be possible that different risk factors are operative in dysplasia and carcinoma in situ than are responsible for development of frank malignancy.

The lack of data from comparable well-defined patient groups and the lack of a consensus on the grading and reproducibility of dysplasia are additional factors that have a negative impact on its predictive value, as is also exemplified by two recent studies. One study reports that a binary system of grading oral epithelial dysplasia may have an increased power in predicting malignant transformation (11), whereas the other indicates that lesions with slight, moderate, severe, and no dysplasia developed carcinoma with similar frequencies (12). Such opposing views attempting to correlate the degree of dysplasia with the likelihood of malignant transformation are frustrating and underscore the need for more precise prognosticators. The potential usefulness of molecular methods will be discussed in the next section.

V. GENETIC CHANGES IN DYSPLASIAS AND THEIR DIAGNOSTIC USEFULNESS

Because of the subjective nature of dysplasia assessment, molecular analysis has been introduced in the field with the aim that it would be helpful in obtaining a more accurate prognosis. Investigations showed that the spectrum of chromosomal changes increases at each histological step from benign hyperplasia to dysplasia to carcinoma in situ to invasive carcinoma, with losses at chromosomes 9p bearing the *p16/p14^{ARF}* tumor-suppressor gene, 3p bearing the *FHIT* tumor-suppressor gene, and 17p bearing the well-known *p53* tumor-suppressor gene already found at the dysplasia stage (13,14). All these data make sense in that they show how malignant transformation of oral epithelial cells into OSCC is associated with loss of tumor-suppressor abilities.

Although preliminary translation of these data in clinical practice has shown that chromosomal losses at loci 3p and 9p occurring in mucosal lesions may evolve into carcinoma, not all lesions, however, with these genetic alterations progress; other changes also play a role: additional chromosomal losses, chromosomal polysomies, suprabasal *p53* protein expression, and loss of expression of fragile histidine triad (15–21). Currently, none of these approaches have found its way into routine diagnostic applications. Moreover, the development of oral cancer may follow different pathways (22–24). This obviously will make the identification of molecular markers that may solve the problem of predicting malignant change complicated.

VI. LEUKOPLAKIA

A. Definition

Leukoplakia is defined as a “white patch” or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except the use of tobacco (25). This time-honored definition may need some updating as there are currently indications that human papilloma virus (HPV) may also play a role (26–29). In this context, it may be useful to mention that in oral cancer and precancer, in contrast with the uterine cervix, overexpression of p16 cannot be equalized with HPV infection (30), neither does this protein qualify as a marker for dysplasia (31,32). This is not surprising as there are a lot of triggers that could cause overexpression of this protein that participates in major tumor suppressor networks disabled in human cancer and influences key physiological processes such as replicative senescence, apoptosis, and stem cell self-renewal (33).

B. Clinical Features

Leukoplakia is a condition associated with a middle-aged and older population, with the vast majority of cases occurring after the age of 40 years. The floor of the mouth is the most common site in smokers, whereas the border of the tongue is a more common site among nonsmokers (34,35).

On visual examination, leukoplakia may vary from a barely evident, vague whiteness on the base of uninflamed, normal-appearing tissue to a definitive white, thickened, leathery, fissured, verrucous, or wart-like lesion (Fig. 13). Red zones may also be seen in some leukoplakias, prompting use of the term “speckled leukoplakia” (Fig. 14). On palpation, some lesions may be soft, smooth, or finely granular in texture. Other lesions may be roughened, nodular, or indurated (34).



Figure 13 White patch in the left cheek. This picture is typical for homogeneous leukoplakia. Histology is needed to determine the nature of the underlying epithelial alterations causing this clinical appearance.



Figure 14 In “speckled” (inhomogeneous) leukoplakia, white areas alternate with red ones. In general, these lesions histologically show more severe epithelial alterations than the homogeneous ones.

C. Pathology

Histological examination of a leukoplakic lesion invariably shows a hyperkeratotic surface, which causes the clinical appearance. The underlying epithelium may show a spectrum of histological appearances that includes either normal epithelium, various grades of dysplasia, or even carcinoma in situ or OSCC. A histological report on a leukoplakic lesion should leave no doubt on the nature of these epithelial histomorphologies (1,34).

D. Differential Diagnosis

The first step in developing a differential diagnosis for a white patch (leukoplakia) in the oral mucosa is determining whether the lesion can be eliminated with gauze or spatula. If the lesion can be removed, it represents a pseudomembranous lesion, fungal colony, or debris.

If there is evidence of bilateral buccal mucosal disease, conditions not to be discussed further in this chapter such as leukedema and white sponge nevus, cheek biting, lichen planus, and lupus erythematosus (LE) should be considered. The latter two can be associated with cutaneous lesions.

If either chronic trauma or tobacco use is excluded in the patient's history and the lesion is predominantly situated at the gingival margin, the white lesion could represent frictional hyperkeratosis. Elimination of a suspected cause then should result in some clinical improvement.

Nonleukoplakic tobacco-induced white lesions of the oral mucosa include nicotine stomatitis and smoker's keratosis, which will be discussed later in this chapter. Also included in a differential diagnosis for tongue leukoplakia would be hairy or geographical tongue.

If the lesion is not removable and is not clinically diagnostic, it can be generally classified as idiopathic, and biopsy becomes mandatory. In extensive lesions, multiple biopsies may be necessary to avoid sampling error. The clinically most heterogeneous (speckled) areas should be included in the biopsy (34).

E. Treatment and Prognosis

There is general clinical consensus that oral leukoplakia should be treated either to alleviate the patient's complaints or to prevent the future development of OSCC (Fig. 15A, B). The latter aim, however, appears to be difficult to attain, considering the previous discussion.

Dysplasia grading in selecting patients at risk for progressing is of debatable value as already outlined. More importantly, prognosis appears to be the size of the lesion as well as its clinical appearance, speckled leukoplakias being more prone to malignant degeneration (12). In fact, in a long-term follow-up study, 15% of cases with nonhomogeneous leukoplakia developed into OSCC as opposed to 3% of those with homogeneous leukoplakia (12).



Figure 15 In an area of (A) homogeneous leukoplakia, (B) a squamous cell carcinoma was diagnosed six months later.

Whether the lateral border of the tongue and the floor of the mouth are high-risk regions for development of malignancy is a debated subject (10,34,36). Sometimes, leukoplakias may regress, especially when patients quit smoking (37).

Treatment may be effective in the removal of a lesion but relapses and adverse effects are common. Moreover, to date, there is no evidence that treatment is effective in preventing malignant transformation (38). In spite of the limited ability of any treatment in preventing malignancy, various intervention modalities have been advocated, such as surgical excision and CO₂-laser surgery. Also, agents such as β -carotene, α -tocopherol, and ascorbic acid have been attempted but until now none has been proven safe and effective in large-scale randomized trials (39).

VII. PROLIFERATIVE VERRUCOUS LEUKOPLAKIA

A. Definition

Proliferative verrucous leukoplakia (PVL) is a variant of leukoplakia that shows white mucosal plaques that virtually always develop nodular, papillary, or verruciform surface projections, that gradually, sometimes rapidly, spreads to encompass large regions of the oral mucosa, and that is associated with a very high rate of malignant transformation (40–43). The cause is unknown. Neither tobacco usage nor infection with HPV has been demonstrated to be of any etiological significance (43–45).

B. Clinical Features

This type of leukoplakia begins in most instances as a simple keratosis, slow growing, persistent, and irreversible, and eventually becomes verrucous in nature (Fig. 16). The diagnosis is determined clinicopathologically and is usually made in retrospect. PVL behaves far more aggressively than other forms of oral leuko-



Figure 16 Proliferative verrucous leukoplakia showing thick, irregular keratotic plaques involving large mucosal areas.

plakia as malignant transformation to verrucous or squamous cell carcinoma is almost always the outcome for patients with PVL (41,43). The aggressiveness is not only demonstrated by a high recurrence rate after surgical excision but also by development of multiple OSCCs (46).

C. Pathology

There is no histological feature that is pathognomonic for PVL. As this disease encompasses a spectrum ranging from flat homogeneous leukoplakia to conventional OSCC with various grades of dysplasia and verrucous carcinoma as intermediate stages, the histopathology of an individual lesion from a patient with PVL may show a morphology compatible with any of these diagnoses, depending on the stage of the disease (Fig. 17). The initial classification in 10 stages has been reduced to four stages: clinically flat leukoplakia without dysplasia, verrucous hyperplasia, verrucous carcinoma, and conventional squamous cell carcinoma (40,42). Probably, the number of stages can be reduced to three as verrucous hyperplasia has much in common with verrucous carcinoma, the only difference being an exophytic growth pattern in verrucous hyperplasia as opposed to an endophytic growth pattern in verrucous carcinoma (42). Therefore, it is debatable if there is any need to make this distinction between verrucous hyperplasia and verrucous carcinoma (47).

D. Differential Diagnosis

The typical clinical appearance of PVL does not leave any room for consideration of another lesion. However, the diagnosis cannot be made unless the patient has developed the complete clinical picture as outlined above.

E. Treatment and Prognosis

Treatment procedures employed for PVL have been surgery, CO₂-laser evaporation, and photodynamic therapy. It is commonly resistant to all forms of therapy. Early recurrence of the lesion in the same area is the rule, usually accompanied by greater extension and by an increase of epithelial changes including dysplasia (40). It has been reported that in case of an HPV-related PVL, the use of an antiviral agent appears to offer a significant enhancement to the surgical management of PVL (48). Recent data denying any etiological significance of HPV, however, make the purported result of this therapeutic approach difficult to understand (44,45).

VIII. ERYTHROPLAKIA

A. Definition

Erythroplakia is the clinical term for “a fiery red patch” that cannot be characterized clinically or pathologically as any other definable lesion (49,50). The term is used analogously to leukoplakia.

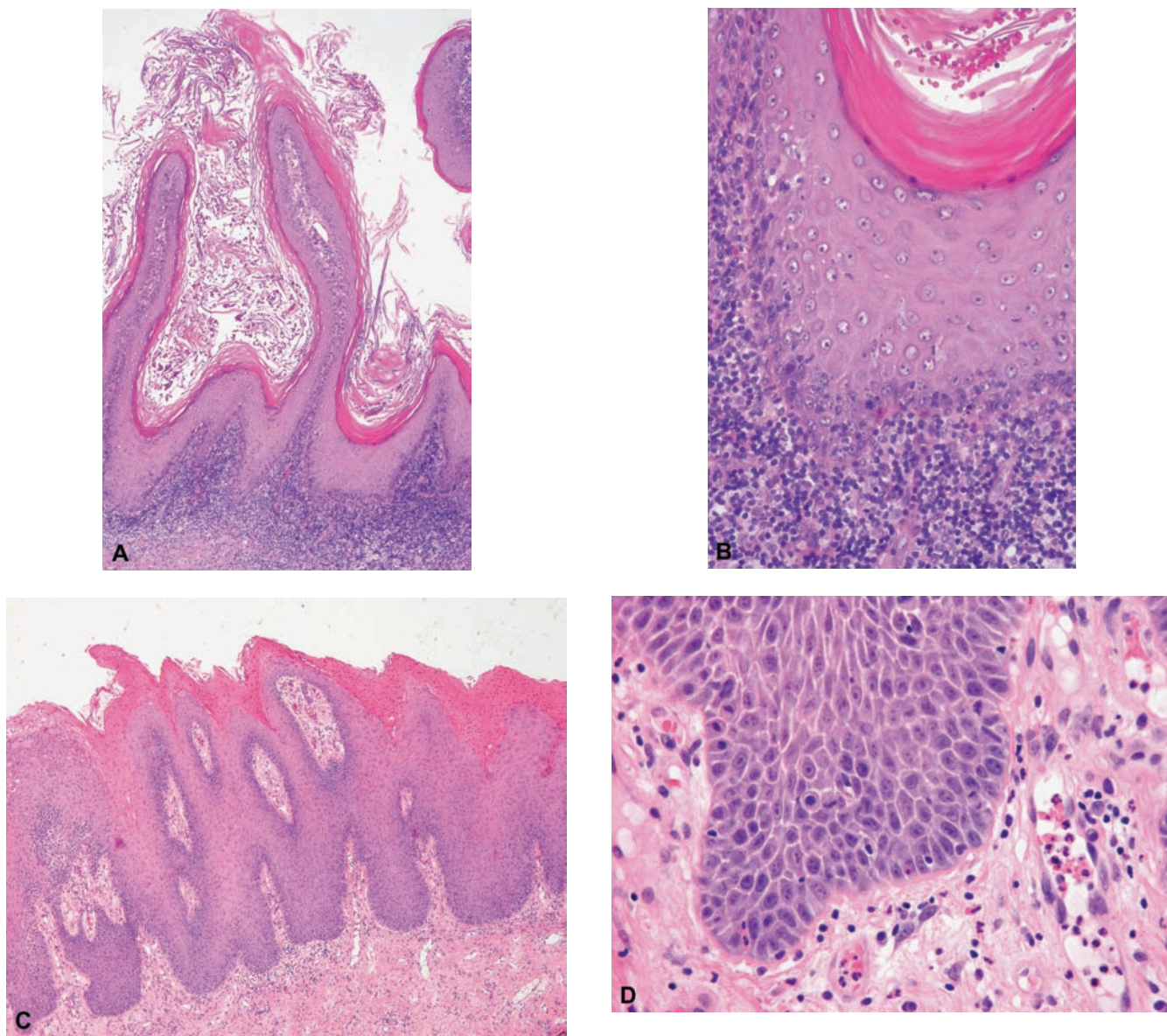


Figure 17 Photomicrographs showing various appearances that may be shown by patients suffering from proliferative verrucous leukoplakia. (A) Papillary epithelial projections covered with a hyperkeratotic surface. (B) Cellular alterations in the epithelium are not very conspicuous [detail from (A)]. (C) Hyperplastic epithelium with a hyperkeratotic surface forming spires. (D) Detail from (C) showing increased mitotic activity and slight cytonuclear atypia.

B. Clinical Features

Erythroplakia is less frequently seen than its leukoplakic counterpart with a prevalence of between 0.02% and 0.83% from different geographical areas. The lesions appear either as a red smooth patch or, alternatively, as an irregular granular patch with fairly well-defined margins with the adjacent mucosa of normal appearance. Sites of occurrence are the buccal mucosa, floor of the mouth, and the soft palate (Fig. 18, 19). The tongue is rarely involved (50). There may be concomitant leukoplakia, which may make the distinction between speckled leukoplakia and erythroplakia equivocal.

Individuals aged between 50 and 70 years are usually affected, and there appears to be no gender predilection.

There is a strong association with tobacco consumption and the use of alcohol (50).

C. Pathology

Histologically, erythroplakia shows invasive OSCC in over 50% of cases, in situ cancer in 40% of cases, and in only 10% of cases mild or moderate dysplasia is observed (50). This high incidence of neoplasia



Figure 18 Localized erythroplakia in the anterior floor of the mouth.



Figure 19 More extensive erythroplakia in the floor of the mouth.

emphasizes the need to take biopsies from each erythroplakic lesion.

D. Differential Diagnosis

The clinical features of erythroplakia may occasionally be shared by several other red lesions. Erythematous candidiasis and atrophic oral lichen planus result in a red mucosal lesion. A more extensive differential diagnosis would include Kaposi's sarcoma, ecchymosis, contact allergic reaction, vascular malformation, or psoriasis. A careful clinical history and examination should distinguish most of these lesions. Biopsy is required if there is any doubt.

E. Treatment and Prognosis

The treatment of choice for erythroplakia is surgical excision, although the effectiveness of this intervention, including laser therapy and cryotherapy, has until now never been analyzed in controlled clinical

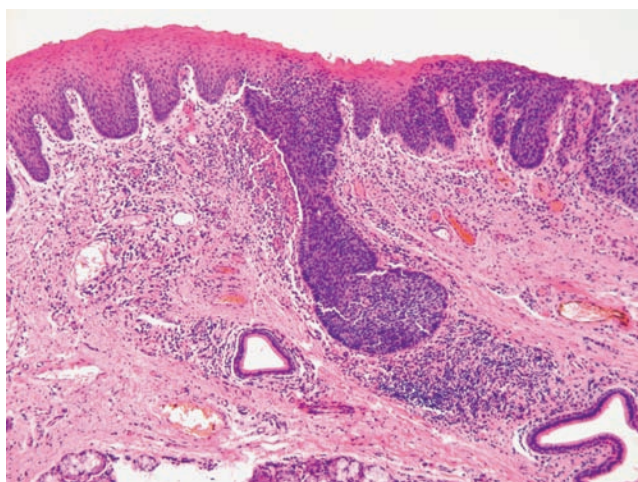


Figure 20 The dysplastic epithelial changes underlying a leukoplakic lesion may extend to deeper levels by replacing duct lining epithelium.

studies. In case of surgical therapy in dysplastic and in situ lesions, it is generally more important to excise widely than deeply because of their superficial nature. However, because the epithelial changes may extend into the salivary gland excretory ducts, the excision should not be too superficial. Extensive histological sampling may be necessary to assess adequately the involvement of ducts (Fig. 20).

Prognosis depends on the underlying histomorphology that ranges from mild dysplasia to OSCC.

IX. NICOTINE STOMATITIS

A. Definition

This is a particular form of keratosis occurring on the palate and seen in pipe or cigar smokers. A related palatal lesion is caused by the habit of placing the lighted end of cigarettes and cigars inside the mouth, which is practiced by certain rural populations in the Indian subcontinent, New Guinea, and the Amazon basin. As the literature does not always draw a sharp distinction between these two modes of tobacco usage, both will be discussed under this heading, emphasizing specific features of each.

B. Clinical Features

Nicotine stomatitis shows raised umbilicated papules (representing blocked palatal mucous glands) with red central depressions (their inflamed duct orifices). These papules are found mainly in the posterior regions of the hard palate and on the soft palate (Fig. 21). The background mucosa may vary from clinically normal to gray leukoplakic (51). When specifically distinguishing between palatal changes induced by smoking versus reverse smoking, the



Figure 21 Clinical picture of nicotine stomatitis. Raised umbilicated papules on a leukoplakic background and with a depressed red center are quite typical for this mucosal lesion.

latter category shows more severe changes than the former. In conventional smokers, palatal pigmentation and erythema are seen, whereas in reverse smokers leukoplakia, mucosal thickening, fissuring, pigmentation, nodularity, and ulceration are common (52,53).

C. Pathology

Histologically, nicotine stomatitis is characterized by hyperkeratosis, acanthosis, and dilatation of the underlying salivary gland ducts that show chronic inflammatory alterations (51,54). Concomitant dysplastic alterations have been reported to occur in nicotine stomatitis induced by reverse smoking (55).

Another tobacco-induced histological alteration, the so-called “chevron-like” keratinization does not occur on the palate and so is not included in the spectrum of histological alterations that characterize nicotine stomatitis (56). This tissue alteration will be discussed more extensively under the heading “Smokeless Tobacco Keratosis” (vide infra).

D. Differential Diagnosis

Because of the characteristics of its appearance and the smoking habits of the patient, hardly any other diagnosis could interfere with diagnosing this mucosal disorder.

E. Treatment and Prognosis

Nicotine stomatitis does not evolve into malignancy in conventional smokers but it may in individuals who smoke reversely (34,55,57). Nevertheless, patients should be encouraged to quit smoking to alleviate the symptoms of nicotine stomatitis as well as to prevent development of mucosal (pre-) malignancies elsewhere in the upper aerodigestive tract. There appears to be no room for surgical intervention unless biopsies have shown concomitant dysplasia.

X. ORAL SUBMUCOUS FIBROSIS

A. Definition

Oral submucous fibrosis (OSF) is a chronic progressive disorder characterized by subepithelial fibrosis that interferes with oral functioning (58,59). Chewing areca nut is the major etiological factor (58).

B. Clinical Features

This disease is rarely seen in western countries but generally occur in India and Southeast Asia. People of any age may be affected. Symptoms include a burning sensation of the oral mucosa, occasional mucosal ulceration, a peculiar marble-like blanching of the mucosa, and palpable fibrous bands of the buccal mucosa, soft palate, and lips (Figs. 22, 23). Fiery red erythroplakic areas are also occasionally present.



Figure 22 Oral submucosal fibrosis. Note limited mouth opening and fibrous white appearance of right cheek mucosa. *Source:* Picture courtesy of Prof. Tien-Yu Shieh and Dr. Connie Yang, Oral Health Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan.



Figure 23 Oral submucosal fibrosis. Note the white appearance of the inner side of the reflected upper lip. *Source:* Picture courtesy of Prof. Tien-Yu Shieh and Dr. Connie Yang, Oral Health Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan.

OSF may occasionally be preceded by or associated with vesicle formation. Rupture of these vesicles leaves small superficial ulcerations. In time the affected mucosa, especially the soft palate and buccal mucosa, loses its resilience and elasticity, with resultant trismus and considerable difficulty in eating (58).

C. Pathology

In cases starting with vesicle formation, it is shown that the vesicles are due to a subepithelial fluid accumulation. The adjacent lamina propria contains eosinophilic granulocytes. More typical, OSF shows the first changes in the connective tissue. Four consecutive stages are distinguished, the disease starting with development of edema and presence of a fibroblastic proliferation as well as an inflammatory infiltrate mainly composed of neutrophilic granulocytes. Blood vessels may be dilated but not unvaried. Then, thickened collagen fibers occur together with juxtaepithelial hyalinization. The fibroblastic response is less pronounced. Blood vessels are more prominent and the inflammatory infiltrate now also contains lymphocytes and occasionally plasma cells. The third stage is characterized by hyalinization of the collagen, edema is disappearing as is the fibroblastic proliferation, and the blood vessels return to a normal diameter or even are constricted because of increased surrounding fibrous tissue. The inflammatory infiltrate is now mainly composed of lymphocytes and plasma cells. In the final stage, the picture is dominated by dense hyalinized collagen replacing the lamina propria (Fig. 24). The overlying epithelium is atrophic with loss of rete pegs, and there may be abnormal keratinization (59).

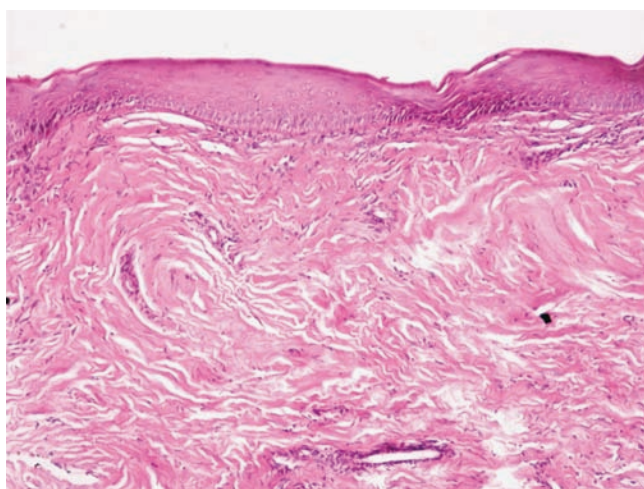


Figure 24 Photomicrograph showing compact collagen covered with a thin squamous epithelial layer typical for oral submucous fibrosis. *Source:* Photomicrograph courtesy of Dr. Yuk-Kwan Chen, Department of Oral Pathology, Kaohsiung Medical University, Kaohsiung, Taiwan.

D. Etiology

The main etiological factors are the constituents of areca nut. These appear to interfere with the deposition and/or degradation of extracellular matrix molecules such as collagen. Inflammatory cytokines also may influence this process of ongoing fibrosis (58).

E. Differential Diagnosis

The clinical differential diagnosis of OSF is limited. Radiation-related subepithelial fibrosis and mucosal scarring secondary to thermal or chemical burns may produce similar clinical features.

F. Treatment and Prognosis

Treatment has included stretching exercises and intralesional injections of corticosteroids. Surgical-releasing procedures likewise have been used. Success has been reported using a combination of both local injections and local surgical excision of bands and submucosal application of placental grafts. All methods of treatment, however, have proved to be of only modest help in this essentially irreversible condition.

The primary importance of OSF lies in its premalignant nature. Epithelial dysplasia in OSF has been reported to vary from 7% to 26% and the malignant transformation rate appears to vary from 7% to 13%. It has been speculated that fibroblastic degeneration and epithelial atrophy form the physical basis for carcinogenic penetration through the epithelium. The restriction or elimination of areca nut use should be attempted and etiological dietary agents should be withdrawn (58).

XI. ACTINIC CHEILITIS

A. Definition

Actinic cheilitis, also known as solar cheilosis, solar cheilitis, or actinic keratosis of the lip, represents an accelerated tissue degeneration of the vermillion portion of the lip, especially the lower lip, secondary to regular and prolonged exposure to sunlight. This particular condition occurs almost exclusively in whites and is especially prevalent in those with a fair skin. It is closely correlated with total cumulative exposure to sunlight and amount of skin pigmentation (60).

B. Clinical Features

The affected vermillion portion of the lips acquires an atrophic, pale-to-silvery gray, glossy appearance, often with fissuring and wrinkling at right angles to the cutaneous-vermillion junction (Fig. 25). In advanced cases, the junction is irregular or totally blurred, with a degree of epidermalization of the vermillion evident. Mottled areas of hyperpigmentation and keratosis are often noted as well as superficial scaling, cracking, erosion, ulceration, and crusting.



Figure 25 Actinic cheilitis characterized by whitish hue on the vermilion border of the lower lip.

C. Pathology

Histologically, actinic cheilitis shows hyperkeratosis, increased thickness of the prickle cell layer, basophilic connective tissue changes, and perivascular inflammatory alterations. Epithelial dysplasia is almost invariably present and varies from mild to severe (61,62).

D. Differential Diagnosis

Although the clinical appearance together with the history of UV exposure makes a diagnosis evident, erosive lichen planus, lupus erythematosus of the lip mucosa, and congenital dyskeratosis have to be mentioned in the differential diagnosis.

E. Treatment and Prognosis

Because of the positive relationship between exposure of UV light and carcinoma (Fig. 26), lip protection is indicated. The use of lip balm containing the sunscreen agent para-aminobenzoic acid (PABA) or its derivatives should be used during periods of sun exposure in high-risk patients. Sun-blocking opaque agents also boost the effectiveness of the balm.



Figure 26 Actinic cheilitis complicated by development of squamous cell carcinoma on the vermilion border of the lower lip.

Chronic sun damage mandates periodic examination and biopsy if ulceration persists or if induration becomes evident. If atypical changes are noted within the epithelium, a vermillionectomy may be performed in association with mucosal advancement to replace the damaged vermillion. Acceptable results are also obtainable with the use of laser evaporation or cryosurgery.

XII. SMOKELESS TOBACCO KERATOSIS

A. Definition

Smokeless tobacco keratosis (snuff pouch, snuff dipper's lesion, tobacco pouch) is a chronic white or gray/translucent mucosal macula localized in areas of direct contact with smokeless tobacco (63). The lesion cannot be scraped off and disappears with cessation of the tobacco habit.

B. Clinical Features

The white lesions of the oral mucosa associated with smokeless tobacco use develop in the immediate area where the tobacco is habitually placed (Fig. 27). The most common area of involvement is the mucobuccal fold of the mandible or the maxilla, in either the incisor or the molar region. The altered mucosa generally has a granular-to-wrinkled appearance. In advanced cases, a heavily folded character may be seen. Less frequently, an erythroplakic or red component may be admixed with the white keratotic component. In a Swedish population using moist snuff, four different clinical degrees of mucosal alterations have been discerned. Degree 1 is characterized by a superficial lesion with a color similar to the surrounding mucosa and a slight wrinkling. In degree 2, there is a superficial whitish or yellowish lesion with wrinkling. In degree 3, a whitish-yellowish-to-brown wrinkled lesion with intervening furrows of normal mucosal color is present together with obvious thickening. Degree 4 shows the same changes as described



Figure 27 Smoker's keratosis induced by snuff dipping in the upper labial fold. *Source:* Picture courtesy of Prof. Jesper Reibel, Department of Oral Medicine, Clinical Oral Physiology, Oral Pathology and Anatomy, School of Dentistry, University of Copenhagen, Copenhagen, Denmark.

for degree 3 with the exception that the furrows have changed their color from normal to red (64). This clinical classification is supported by corresponding histological alterations as outlined below.

C. Pathology

Histological changes in smokeless tobacco users include hyperparakeratosis, hyperorthokeratosis, a pale eosinophilic zone of hyperkeratosis, and basal cell hyperplasia (65,66). Moreover, a particular keratinization pattern consisting of parakeratinized streaks with an appearance similar to a pine tree, the so-called chevron-like pattern of keratinization, does occur, this feature being part of the mucosal changes associated with the use of smokeless tobacco (Fig. 28) (56,65) as well as appearing as a result of other types of tobacco usage (56). Following are the various histological alterations seen in Swedish snuff dippers that correspond to the clinical alterations as detailed above. In degree 1 lesions, there is slight inflammation but no epithelial changes. Degree 2 shows a thickened surface layer of the epithelium with or without an accompanying surface of necrosis. A considerably thickened surface layer composed of vacuolated cells and chevron-type keratinization characterizes degree 3 clinical mucosal alterations, and in degree 4, a marked thickening of the surface layer may be accompanied

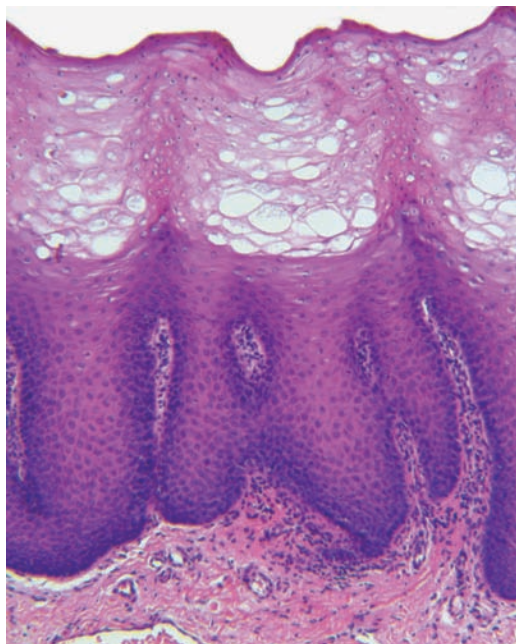


Figure 28 Epithelial alterations due to snuff dipping. Note the specific chevron-like keratinization and the band of pale cells in the upper part of the epithelium. *Source:* Photomicrograph courtesy of Prof. Jesper Reibel, Department of Oral Medicine, Clinical Oral Physiology, Oral Pathology and Anatomy, School of Dentistry, University of Copenhagen, Copenhagen, Denmark.

by areas of atrophy and inflammation (67). Epithelial dysplasia does not form part of the spectrum of histological alterations shown in Swedish moist snuff users (67). In other populations, it may occasionally occur (66). It is however debatable if such lesions with dysplasia should be considered as smoker's keratosis or should be placed in the category of leukoplakia. Probably, it is wise to reserve the term "smoker's keratosis" for lesions because of the use of smokeless tobacco and with the typical histological appearances as outlined above and to put any tobacco-induced lesion that combines hyperkeratosis with dysplastic epithelial alterations within the category of leukoplakia.

D. Differential Diagnosis

Confusing smoker's keratosis with other oral mucosal disorders with a whitish appearance can easily be avoided when taking into account the patient's history and habits. In doubtful cases, histological examination is indicated to rule out more serious epithelial alterations.

E. Treatment and Prognosis

With discontinuation of smokeless tobacco use, some lesions may disappear after several weeks, indicative of an excellent prognosis (67). Persistent lesions should be removed and examined histologically. Moreover, patients who use smokeless tobacco have a slightly increased risk for development of oral cancer, this also warranting follow-up for those who persist in this habit (66,68,69). The risk for malignant change, however, may vary among patient populations, type of smokeless tobacco used, and mode of application, as for some populations, this risk has been reported to be zero (67). These conflicting data may be due to confusing genuine smoker's keratosis with leukoplakia, an issue already alluded to in the previous text devoted to the pathological features.

XIII. LICHEN PLANUS

Lichen planus typically presents as intertwining thin strands or streaks of white keratosis (Wickham's striae) of the bilateral buccal mucosa. Its potential for malignant transformation is questioned as it is stated that reports of malignant progression could be due to confounding lichen planus with the so-called lichenoid dysplasia, a lesion probably representing leukoplakia but resembling lichen planus clinically and histologically (70–72).

REFERENCES

1. Bouquot JE, Speight PM, Farthing PM. Epithelial dysplasia of the oral mucosa – Diagnostic problems and prognostic features. *Curr Diagn Pathol* 2006; 12(1):11–21.

2. Lotan R. Are we ready to use surrogate end points and surrogate tissues to evaluate response to chemopreventive and therapeutic intervention? *Clin Cancer Res* 2000; 6(6):2126–2128.
3. Kopelovich L, Henson DE, Gazdar AF, et al. Surrogate anatomic/functional sites for evaluating cancer risk: an extension of the field effect. *Clin Cancer Res* 1999; 5(12):3899–3905.
4. Gale N, Pilch BZ, Sidransky D, et al. Epithelial precursor lesions. In: Barnes L, Eveson JW, Reichart P, et al., eds. *WHO Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005: 140–143, 177–179.
5. Gale N, Zidar N. Benign and potentially malignant lesions of the squamous epithelium and squamous cell carcinoma. In: Cardesa A, Slootweg PJ, eds. *Pathology of the Head and Neck*. Berlin Heidelberg: Springer, 2006:4–13.
6. Zerdoner D. The Ljubljana classification – its application to grading oral epithelial hyperplasia. *J Craniomaxillofac Surg* 2003; 31(2):75–79.
7. Driemel O, Hertel K, Reichert TE, et al. Current classification of precursor lesions of oral squamous cell carcinoma principles of the WHO classification 2005. *Mund Kiefer Gesichtschir* 2006; 10(2):89–92.
8. Crissman JD, Zarbo RJ. Dysplasia, in situ carcinoma, and progression to invasive squamous cell carcinoma of the upper aerodigestive tract. *Am J Surg Pathol* 1989; 13 (suppl 1):5–16.
9. Scully C, Sudbo J, Speight PM. Progress in determining the malignant potential of oral lesions. *J Oral Pathol Med* 2003; 32(5):251–256.
10. Reibel J. Prognosis of oral pre-malignant lesions: significance of clinical, histopathological, and molecular biological characteristics. *Crit Rev Oral Biol Med* 2003; 14(1): 47–62.
11. Kujan O, Oliver RJ, Khattab A, et al. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. *Oral Oncol* 2006; 42(10):987–993.
12. Holmstrup P, Vedtofte P, Reibel J, et al. Long-term treatment outcome of oral premalignant lesions. *Oral Oncol* 2006; 42(5):461–474.
13. Kim MM, Califano JA. Mini review. Molecular pathology of head-and-neck cancer. *Int J Cancer* 2004; 112(4):112, 545–553.
14. Bremner JF, Braakhuis BJM, Ruijter-Schippers HJ, et al. A noninvasive genetic screening test to detect oral preneoplastic lesions. *Lab Invest* 2005; 85(12):1481–1488.
15. Mao L, Lee JS, Fan YH, et al. Frequent microsatellite alterations at chromosomes 9p21 and 3p14 in oral premalignant lesions and their value in cancer risk assessment. *Nat Med* 1996; 2(6):682–685.
16. Rosin MP, Cheng X, Poh C, et al. Use of allelic loss to predict malignant risk for low-grade oral epithelial dysplasia. *Clin Cancer Res* 2000; 6(2):357–362.
17. Lee JJ, Hong WK, Hittelman WN, et al. Predicting cancer development in oral leukoplakia: ten years of translational research. *Clin Cancer Res* 2000; 6(5):1702–1710.
18. Partridge M, Pateromichelakis S, Phillips E, et al. A case-control study confirms that microsatellite assay can identify patients at risk of developing oral squamous cell carcinoma within a field of cancerization. *Cancer Res* 2000; 60(14):3893–3898.
19. Cruz IB, Snijders PJF, Meijer CJ, et al. p53 immunorepression in non-malignant oral mucosa adjacent to oral squamous cell carcinoma: potential consequences for clinical management. *J Pathol* 2000; 191(2):132–137.
20. Cruz I, Napier SS, Waal I van der, et al. Suprabasal p53 immunorepression is strongly associated with high grade dysplasia and risk for malignant transformation in potentially malignant oral lesions from Northern Ireland. *J Clin Pathol* 2002; 55(2):98–104.
21. Kujan O, Oliver R, Roz L, et al. Fragile histidine triad expression in oral squamous cell carcinoma and precursor lesions. *Clin Cancer Res* 2006; 12(22):6723–6729.
22. Hunter KD, Parkinson EK, Harrison PR. Profiling early head and neck cancer. *Nat Rev Cancer* 2005; 5(2): 127–135.
23. Hunter KD, Thurlow JK, Fleming J, et al. Divergent routes to oral cancer. *Cancer Res* 2006; 66(15):7405–7413.
24. Noutomi Y, Oga A, Uchida K, et al. Comparative genomic hybridization reveals genetic progression of oral squamous cell carcinoma from dysplasia via two different tumorigenic pathways. *J Pathol* 2006; 210(1):67–74.
25. Axell T, Pindborg JJ, Smith CJ, et al. Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18–21 1994. International Collaborative Group on Oral White Lesions. *J Oral Pathol Med* 1996; 25(2):49–54.
26. Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. *J Clin Virol* 2005; 32(suppl 1):S59–S66.
27. Cianfriglia F, Gregorio Di DA, Cianfriglia C. Incidence of human papillomavirus infection in oral leukoplakia. Indications for a viral aetiology. *J Exp Clin Cancer Res* 2006; 25(1):21–28.
28. Cunningham LL Jr., Pagano GM, Li M, et al. Overexpression of p16INK4 is a reliable marker of human papillomavirus-induced oral high-grade squamous dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102(1):77–81.
29. Furrer VE, Benitez MB, Furnes M, et al. Biopsy vs. superficial scraping: detection of human papillomavirus 6, 11, 16, and 18 in potentially malignant and malignant oral lesions. *J Oral Pathol Med* 2006; 35(6):338–344.
30. Nemes JA, Deli L, Nemes Z, et al. Expression of p16 (INK4A), p53, and Rb proteins are independent from the presence of human papillomavirus genes in oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102(3):344–352.
31. Gologan O, Barnes EL, Hunt JL. Potential diagnostic use of p16INK4A, a new marker that correlates with dysplasia in oral squamoproliferative lesions. *Am J Surg Pathol* 2005; 29(6):792–796.
32. Bradley KT, Budnick SD, Logani S. Immunohistochemical detection of p16INK4a in dysplastic lesions of the oral cavity. *Mod Pathol* 2006; 19(10):1310–1316.
33. Gil J, Peters G. Regulation of the INK4b-ARF-INK4a tumour suppressor locus: all for one or one for all. *Nat Rev Mol Cell Biol* 2006; 7(9):667–677.
34. Waal I van der, Schepman KP, Meij EH van der, et al. Oral leukoplakia: a clinicopathological review. *Oral Oncol* 1997; 33(5):291–301.
35. Schepman KP, Bezemer PD, Meij EH van der, et al. Tobacco usage in relation to the anatomical site of oral leukoplakia. *Oral Dis* 2001; 7(1):25–27.
36. Schepman KP, Meij EH van der, Smeele LE, et al. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncol* 1998; 34(4): 270–275.
37. Roosaar A, Yin L, Johansson ALV, et al. A long-term follow-up study on the natural course of oral leukoplakia in a Swedish population-based sample. *J Oral Pathol Med* 2007; 36(2):78–82.
38. Lodi G, Sardella A, Bez C, et al. Interventions for treating oral leukoplakia. *Cochrane Database Syst Rev* 2006; 18(4): CD001829.

39. Brown KS, Kane MA. Chemoprevention of squamous cell carcinoma of the oral cavity. *Otolaryngol Clin North Am* 2006; 39(2):349–363.
40. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol* 1985; 60(3):285–298.
41. Silverman S Jr., Olson JA. Proliferative verrucous leukoplakia: a follow-up study of 54 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84(2):154–157.
42. Batsakis JG, Suarez P, El-Naggar AK. Review. Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol* 1999; 35(4):354–359.
43. Reichart PA, Philipsen HP. Proliferative verrucous leukoplakia. Report of five cases. *Mund Kiefer Gesichtschir* 2003; 7(3):164–170.
44. Campisi G, Giovanelli L, Ammatuna P. Proliferative verrucous vs conventional leukoplakia: no significantly increased risk of HPV infection. *Oral Oncol* 2004; 40(8):835–840.
45. Bagan JV, Jimenez Y, Murilli J. Lack of association between proliferative verrucous leukoplakia and human papillomavirus infection. *J Oral Maxillofac Surg* 2007; 65(1):46–49.
46. Bagan JV, Murillo J, Poveda R, et al. Proliferative verrucous leukoplakia: unusual locations of oral squamous cell carcinomas, and field cancerization as shown by the appearance of multiple OSCCs. *Oral Oncol* 2004; 40(4): 440–443.
47. Slootweg PJ, Muller H. Verrucous hyperplasia or verrucous carcinoma. An analysis of 27 patients. *J Maxillofac Surg* 1983; 11(1):13–19.
48. Femiano F, Gombos F, Scully C. Oral proliferative verrucous leukoplakia (PVL); open trial of surgery compared with combined therapy using surgery and methisoprinol in papillomavirus-related PVL. *Int J Oral Maxillofac Surg* 2001; 30(4):318–322.
49. Pindborg JJ, Reichart PA, Smith CJ, et al. *Histological Typing of Cancer and Precancer of the Oral Mucosa*. 2nd ed. Berlin: Springer, 1997.
50. Reichart PA, Philipsen HP. Oral erythroplakia—a review. *Oral Oncol* 2005; 41(6):551–561.
51. Schwartz DL. Stomatitis nicotina of the palate; report of two cases. *Oral Surg Oral Med Oral Pathol* 1965; 20(Sep):306–315.
52. Mercado-Ortiz G, Wilson D, Jiang DJ. Reverse smoking and palatal mucosal changes in Filipino women. Epidemiological features. *Aust Dent J* 1996; 41(5):300–303.
53. Ortiz GM, Pierce AM, Wilson DF. Palatal changes associated with reverse smoking in Filipino women. *Oral Dis* 1996; 2(3):232–237.
54. Quigley LF, Cobb CM, Hunt EE. Reverse cigarette smoking in Caribbeans: clinical, histologic, and cytologic observations. *J Am Dent Assoc* 1966; 72(4):867–873.
55. Mehta FS, Jalnawalla PN, Daftary DK, et al. Reverse smoking in Andhra Pradesh, India: variability of clinical and histologic appearances of palatal changes. *Int J Oral Surg* 1977; 6(2):75–83.
56. Pindborg JJ, Reibel J, Roed-Peterson B, et al. Tobacco-induced changes in oral leukoplakic epithelium. *Cancer* 1980; 45(9):2330–2336.
57. Eb MM van der, Leyten EM, Gavarasana S, et al. Reverse smoking as a risk factor for palatal cancer: a cross-sectional study in rural Andhra Pradesh, India. *Int J Cancer* 1993; 54(5):754–758.
58. Tilakaratne WM, Klinikowski MF, Saku T, et al. Oral submucous fibrosis: review on aetiology and pathogenesis. *Oral Oncol* 2006; 42(6):561–568.
59. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol* 1966; 22(6):764–779.
60. Visscher JG, Waal I van der. Etiology of cancer of the lip. A review. *Int J Oral Maxillofac Surg* 1998; 27(3):199–203.
61. Kaugars GE, Pillion T, Svirsky JA, et al. Actinic cheilitis. A review of 152 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 88(2):181–186.
62. Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. *Oral Dis* 2004; 10(4):212–216.
63. Taybos G. Oral changes associated with tobacco use. *Am J Med Sci* 2003; 326(4):179–182.
64. Andersson G, Axell T, Larsson A. Clinical classification of Swedish snuff dippers' lesions supported by histology. *J Oral Pathol Med* 1991; 20(6):253–257.
65. Daniels TE, Hansen LS, Greenspan JS, et al. Histopathology of smokeless tobacco lesions in professional baseball players. Associations with different types of tobacco. *Oral Surg Oral Med Oral Pathol* 1992; 73(6):720–725.
66. Warnakulasuriya KAAS, Ralhan R. Clinical, pathological, cellular and molecular lesions caused by oral smokeless tobacco—a review. *J Oral Pathol Med* 2007; 36(2):63–77.
67. Larsson A, Axell T, Andersson G. Reversibility of snuff dippers' lesion in Swedish moist snuff users: a clinical and histologic follow-up study. *J Oral Pathol Med* 1991; 20(6):258–264.
68. Rodu B, Jansson C. Smokeless tobacco and oral cancer. A review of the risks and determinants. *Crit Rev Oral Biol Med* 2004; 15(5):252–263.
69. Warnakulasuriya S. Smokeless tobacco and oral cancer. *Oral Dis* 2004; 10(1):1–4.
70. Meij EH van der, Schepman KP, Smeele LE, et al. A review of the recent literature regarding malignant transformation of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 88(3):307–310.
71. Meij EH van der, Schepman KP, Waal I van der. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(2):164–171.
72. Meij EH van der, Mast H, Waal I van der. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. *Oral Oncol* 2007; 43(8):742–748.

Cancer of the Oral Cavity and Oropharynx

Samir K. El-Mofty and James S. Lewis, Jr.

Department of Pathology and Immunology, Washington University, St. Louis, Missouri, U.S.A.

I. INTRODUCTION

The most common type of cancer affecting the oral cavity and oropharynx is squamous cell carcinoma (SCC), which is estimated to constitute approximately 94% of all oral malignancies (1). Because of this dominance, the term "oral cancer" is used synonymously with oral SCC (2). Others, less commonly encountered carcinomas, are malignant melanoma and neuroendocrine carcinoma, which will be discussed later in this chapter. Carcinomas of minor salivary glands are detailed in the respective chapter in the text.

SCC occurring at different anatomic subsites in the oral cavity and oropharynx vary considerably in their epidemiologic, demographic, pathologic, and clinical features. Consequently, it is not possible to address these various tumors collectively. The following discussion will address in details each individual carcinoma by its respective site of incidence. The following is a list of these entities:

SCC of the oral cavity:

1. SCC of the lip
2. SCC of the buccal mucosa
3. SCC of the floor of the mouth (FOM) and oral tongue (OT)
4. SCC of the gingival and alveolar mucosa
5. SCC of the hard palate
6. SCC of the retromolar trigon

SCC of the oropharynx:

1. SCC of soft palate and uvula
2. SCC of the oropharyngeal wall
3. SCC of tonsils and base of tongue

Keratinizing squamous cell carcinoma (KSCC) is the prototype and the most common SCC. However, there is a range of distinct morphologic variants, of this neoplasm, that are of clinical significance. Differences in clinical, pathologic, demographic and epidemiologic features of these variants will be addressed here. The following is a list of these variants:

1. Nonkeratinizing squamous cell carcinoma (NKCa)
2. Basaloid squamous carcinoma (BSC)
3. Adenosquamous carcinoma (ASC)

4. Adenoid squamous carcinoma
5. Verrucous carcinoma (VC)
6. Papillary squamous carcinoma
7. Spindle cell (sarcomatoid) carcinoma

II. ANATOMY OF THE ORAL CAVITY AND OROPHARYNX

According to the American Joint Committee on Cancer Staging, the oral cavity extends from the skin vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papillae of the tongue below (Fig. 1). It can be divided into eight areas: lip mucosa, buccal mucosa, lower alveolar ridge, upper alveolar ridge, retromolar gingival [retromolar trigone (RMT)], FOM, hard palate, and anterior two-thirds of the tongue (the OT) (Figs. 1, 2).

The oropharynx extends from the plane of the hard palate superiorly to the plane of the hyoid bone inferiorly (Fig. 3), and is continuous with the oral cavity through an opening called the faucial isthmus. The oropharynx is separated from the oral cavity by the junction of the soft and hard palates superiorly, the line of the circumvallate papillae inferiorly, and the anterior pillars of the fauces laterally.

The oropharynx encompasses three main regions—the palatine arch, the base of tongue, and the lateral and posterior pharyngeal walls. The palatine arch constitutes the inferior surface of the soft palate and uvula, the palatine tonsils, and their anterior and posterior pillars (Fig. 4). Although the RMT is technically a component of the oral cavity, carcinomas in this location often involve adjacent oropharyngeal sites and behave more like oropharyngeal tumors (Fig. 4).

III. EPIDEMIOLOGY AND ETIOLOGY

Oral cancer is an important global health concern accounting for an estimated 275,000 cases and 128,000 deaths annually (3–5). Cancer of the mouth and pharynx ranks sixth overall in the world. Its incidence varies markedly by geographic region.

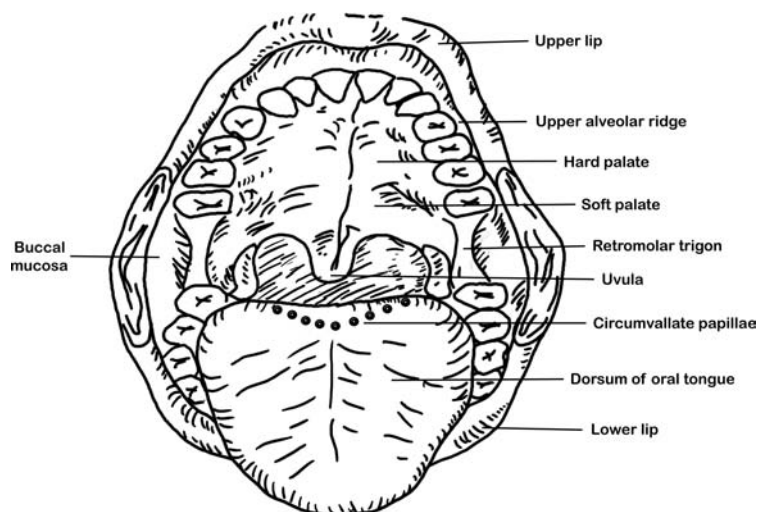


Figure 1 Diagram showing the relationships of the oral cavity anatomic subsites.

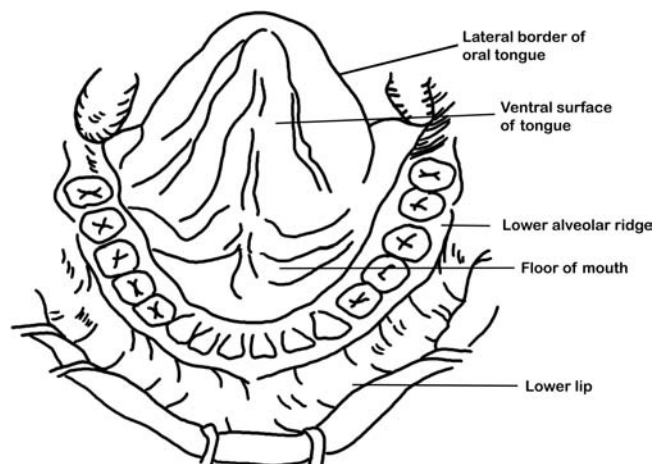


Figure 2 Diagram illustrating the anatomic relationship of the OT, FOM, alveolar ridge, and lower lip. Abbreviations: OT, oral tongue; FOM, floor of the mouth.

Two-thirds of all cases are observed in developing countries. The Indian subcontinent accounts for one-third of the global burden. Men are affected two-to-three times as often as women. The oral cavity/oropharynx is the third most common site for cancer among males in developing countries (3–5). However, the incidence of oral cancer for women can be equal to, or even greater than, that of men in high incidence areas where both sexes are equally exposed to the same risk factors (4).

In the United States, approximately 24,000 men and 10,000 women are diagnosed with oral and oropharyngeal carcinomas annually, representing 3.2% of all newly diagnosed cancers (6,7). The majority of the carcinomas develop predominantly between the fifth and eight decades of life. Women tend to develop the

disease 10 years later than men (8). Changes in incidence-age have been observed during an approximately 30-year period. Using the 1973–2001 surveillance, epidemiology, and end results (SEER) database, a statistically significant increase in oropharyngeal carcinoma in young patients of 20 to 44 years was observed. No similar increase was evident in oral SCC (9). Another study found a significant annual increase in tonsillar SCC in men, but not women, who are younger than 60 years. Again, no similar increase was observed in oral nontonsillar sites (10). The total incidence rates of oral cavity and oropharynx are found to be higher among blacks than whites. Considerable racial and ethnic differences in the prevalence of oral/pharynx cancer may be related to social and cultural practices as well as socioeconomic factors.

Risk factors for oral/pharynx cancer can be generally classified into several categories including chemical carcinogens, oncogenic viruses, sunlight, oral hygiene, nutritional factors, genetic predisposition, and immunocompromise.

A. Chemical Carcinogens

The most important chemical carcinogens are related to tobacco and alcohol abuse. Through a large number of epidemiologic studies, a strong link has been established between the use of tobacco and oral/pharynx SCC. Alcohol is an independent risk factor for the disease, but it may have synergistic effect when combined with tobacco (7). The risk of development of cancer is three to nine times greater in those who smoke or drink, and as much as 100 times greater in those who smoke and drink heavily, than those who neither smoke nor drink (11). It has been estimated that approximately 75% of oral cancers are related to prolonged and heavy smoking and alcohol abuse (12). Cigar and pipe smoking pose similar risk as cigarette smoking. Tobacco and alcohol abuse has been

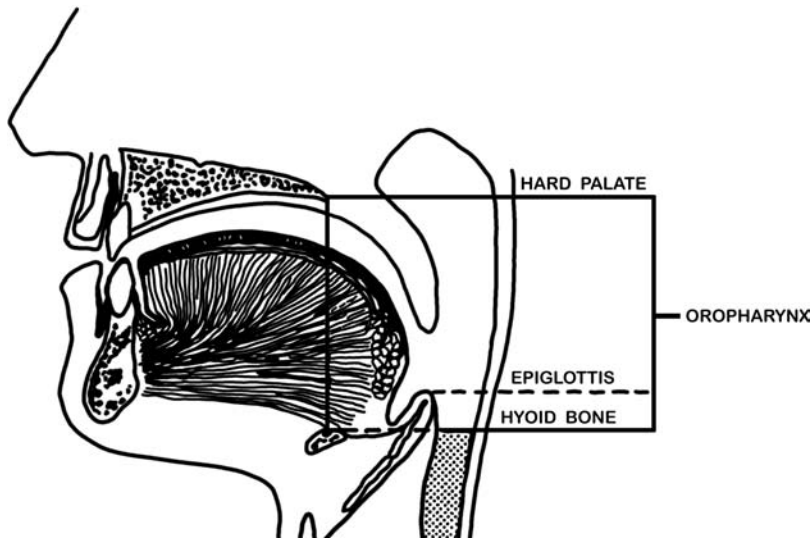


Figure 3 Anatomical boundaries of the oropharynx as defined by the American Joint Committee on Cancer staging. The tip of the epiglottis is considered the inferior border of the oropharynx by some surgeons.



Figure 4 Diagram showing the relationship of the RMT to the various components of the oropharynx. Abbreviation: RMT, retromolar trigone.

implicated in the higher rates and earlier onset of cancer among men in general and African American men in particular (8,12,13).

In addition to cigarettes, cigars, and pipes, tobacco is commonly smoked in other forms, in particular in parts of India and South Asia. Bidi, made of low-grade tobacco wrapped in tender leaf tobacco is popular among rural folk and urban poor. The concentrations of nicotine, tar, and other toxic agents in the smoke are higher in bidi than other cigarettes, with a higher risk for development of oral cancer (14). Reverse chutta smoking, with the lighted end of the cigar placed inside the mouth, is associated with particularly high rates of oral cancer of the palatal mucosa (1,15), a site with otherwise very low cancer incidence.

The primary cause of the very high incidence of oral cancer in South Asia is, however, the widespread habit of chewing betel quid or paan and related Areca nut use. An estimated 200 to 400 million people practice the habit worldwide (16). The components of the betel quid vary between different populations, but the main ingredients are the leaf of the vine *Piper betel*—which is not botanically related to the Betel palm, Areca nut, slaked lime (calcium hydroxide), and spices,

which may include cloves and cardamom. Betel chewing is a tradition that goes back thousands of years. Tobacco was added to betel quid sometime after its introduction to South Asia by Europeans in the seventeenth century. Although Areca nut is carcinogenic in itself, the addition of tobacco increased the risk (17,18).

As in the case of smoking, the risk for oral cancer is dependent on dose and duration of use (19). Much of the tobacco consumption in the world is without combustion. In India, up to 40% of tobacco use is in smokeless forms, mostly of the species *Nicotiana rustica*, while most smoking tobacco is *Nicotiana tabacum* (20). Samples of *N. rustica* have been found to contain higher concentrates of tobacco-specific nitrosamines than *N. tabacum* (21). The tobacco is placed in direct contact with the mucosa. In the developing countries, tobacco is mostly consumed mixed with other ingredients, in addition to betel nut. Lime, molasses, oils, and spices are used. Snuff is common in Scandinavia and the United States. Tobacco is also prepared in blocks or flakes for chewing. “Snuff dipper cancer” described in the southeastern United States is due to the habit of placing snuff in the labial sulcus (22,23). Females in this geographic area have high prevalence of snuff dipping and oral cancer (24).

Traditional values in some countries do not favor smoking by women and the young, but there is no such taboo against using smokeless tobacco. Most women who use tobacco use it in its smokeless form. The acquisition of tobacco habits, in whatever form, starts at an early age. In one study, one-third to one-half of children younger than 10 years in three rural areas in India had experimented with smoking or smokeless tobacco (25). Children have been known to choke to death on betel nuts. Pakistan's new laws forbid the selling of betel nut to children younger than five years.

More than 300 carcinogens have been identified in tobacco smoke or in its water-soluble components that will leach into saliva (26). The most important of these is the aromatic hydrocarbon benz-pyrene and other tar derivatives as well as the tobacco-specific nitrosamines such as nitroso-nor-nicotine (NNN), nitrosopyrrolidine (NPYR), nitrosodimethylamine. These aromatic hydrocarbons are identifiable in tobacco smoke as well as in smokeless tobacco. They damage DNA by producing adducts, principally O⁶-methylguanine.

Metabolism of these carcinogens usually involves oxygenation by p450 enzymes in cytochromes, and their conjugation, in which the enzyme glutathione S transferase (GST) is involved. Polymorphism of the p450 and GST genes is under active study in search of genetic markers of susceptibility to head and neck cancer and other tobacco-related cancers (27).

Alcohol is the second major risk factor for oral cancer. In the West, 75% to 80% of patients frequently consume alcohol. For nonsmokers, it is the most important risk factor. If above 30 g of alcohol is consumed per day, the risk increases linearly with the amount of alcohol consumed (28,29). As mentioned before, people who smoke and drink have much greater risk of oral cancer than those who only smoke or drink. The risk in all cases is dose dependent.

Pure ethanol has never been shown to be carcinogenic in vitro or in animal studies (30). It is presumed to act in concert with other, more direct carcinogens, so called congeners that are found in the liquor, or from other sources such as tobacco. Nevertheless, alcohol drinking alone is an independent risk for upper aerodigestive tract carcinoma (29).

The increase in oral cancer in the Western world has been related to rising alcohol use. In England and Wales, alcohol consumption more than doubled during the second half of the 20th century, which closely matched oral cancer mortality and, by inference, incidence. There is strong circumstantial evidence that alcohol rather than tobacco is the major factor in the observed trend (4,31). Similar data have been reported from Denmark (32). All forms of alcoholic drinks are dangerous if heavily consumed with evidence for the role of beer, wine, and spirits (12,33–36). The risk becomes detectable when consumption exceeds 50 drinks per week.

In 1979, a combined case-control study and case series raised concern that alcohol-containing mouthwash is a risk for oral/pharyngeal cancer (37). More recently, extensive reviews of epidemiologic studies on

the subject did not corroborate earlier reports. It is concluded that the risk of developing oral cancer because of the use of alcohol-containing mouthwash is unlikely (38). Interestingly, however, dental products such as toothpaste and mouthwash containing sanguinarine (such as Viadent), which is the principle alkaloid extract of the bloodroot plant (*Sanguinaria Canadensis* L.), an antibacterial agent, is found to increase the risk of leukoplakia of the maxillary vestibule (39,40).

B. Ultraviolet Light

Chronic exposure to sunlight (actinic radiation) is considered to be the most important factor in causation of lip cancer, the vast majority of which occurs in the lower lip (41–46). This proposal is supported by the observations that cancer of the lip is more common in individuals who have fair complexion and who are more exposed to sunlight because of outdoor occupations or who live near the equator. The propensity of the lip vermilion border for solar damage is attributable to lack of a pigmentary layer that protects against UV radiation (47). Other risk factors may play a role in the causation of cancer of the lip, most notably pipe smoking (45,48–50). It is suggested that the heat and trauma of the pipe stem as well as the tobacco combustion products may play a role in the induction of malignancy.

C. Oncogenic Viruses

Accumulating evidence during the last two decades has linked high-risk human papillomavirus (HPV), particularly type 16, with some upper aerodigestive tract carcinomas. The virus, which is a prerequisite for cervical cancer, is also found to be an important etiologic factor for a distinct, nonkeratinizing type of SCC, which occurs in the oropharynx and more specifically in the palatine tonsils and base of tongue. The virus is very rarely identified in carcinoma of the oral cavity proper (51–57). Substantial epidemiologic, clinical, microscopic, and molecular evidence strongly support the connection between oropharyngeal cancer and HPV. HPV-related oropharyngeal carcinoma is identified in subjects, with or without the established risk factors of tobacco and alcohol use (51–57). No other type of oncogenic viruses has been convincingly shown to play a strong and direct role in the etiology of oral/pharyngeal SCC.

D. Dental Factors and Chronic Inflammation

An association between poor oral hygiene and poor dentition and oral cancer has been reported in several studies (4,36,58,59). Experimental evidence in animals shows localization of chemical carcinogens-induced tumors to the sites of repeated mucosal traumatization. An increase in yield and shortened latent period for the development of the cancers are also observed in these sites (4). Clinical observations in human cases describe carcinomas developing at sites of chronic trauma caused by a broken teeth or ill-constructed dental

appliances (4,59,60). It is certain that the role of inflammation, whether caused by poor hygiene, infections or mechanical trauma, in the etiology of carcinoma, is compounded by known carcinogens such as tobacco and alcohol abuse, nutritional deficiencies, and other risks. However, during the current decade, the possibility of a connection between chronic inflammation and cancer has received intensive scrutiny and has moved to center stage in cancer research. It has been stated by some researchers that “genetic damage is the match that lights the fire of the malignant process, and inflammation is the fuel that feeds it” (61). Recent clinical studies and experimental mouse models highlight a paradoxical role for the immune system as crucial regulator of cancer development (62). Tumor-associated macrophages (TAM), which are ubiquitous in the stroma of virtually all tumors, release a distinct repertoire of growth factors, cytokines, chemokines, and enzymes that are known to regulate tumor growth, angiogenesis, invasion, and/or metastasis (61–64).

The risk for malignancy associated with oral lichen planus, a chronic inflammatory dermatologic disease, remains a subject of debate (1,65). Candidal hyphae are commonly observed to superficially invade premalignant and malignant oral lesions. That such an association may be causally related, rather than an effect of the malignant process, has been suggested (4,63,66). Some strains of candida were shown to produce hyperkeratotic lesions in the dorsal rat tongue (1). In other studies, it was demonstrated that some strains of *Candida albicans* produce the chemical carcinogen nitrosamine from dietary amines substrates (1,67).

E. Nutritional Deficiencies

Numerous studies report a significant preventive effect of proper diet on oral/pharyngeal cancer (68–72). The antioxidant or free radical-scavenging vitamins A, C, and E as well as iron and trace elements, such as zinc and selenium, share a proven protective effect. High incidence of upper gastrointestinal tract carcinoma is seen in middle-aged women with chronic iron deficiency anemia, glossitis, and mucosal atrophy, a condition known as the Plummer-Vinson syndrome. In animals rendered iron deficient by venesection and low-iron diets, there developed epithelial atrophy and increased cancer risk, which was clearly shown when such animals were challenged with chemical carcinogens (71).

An important study in China found a strong protective effect for carotenoid and vitamin C and fiber intake in oral cancer risk (72).

F. Altered Immunity

A similarity in the pattern of increased risk for cancer in both HIV/AIDS populations and immunosuppressed organ transplant recipients suggests that the immune deficiency rather than other risk factors for cancer is responsible for the increased risk (73). In both of these two populations, there is significant increase of incidence, predominantly in cancers with known infectious cause (73–75). These include all three types

of AIDS-defining cancers: Kaposi’s sarcoma, non-Hodgkin’s lymphoma, and cervical cancer as well as all HPV-related cancers and Hodgkin’s lymphoma. An increased incidence in oral/pharyngeal cancer is observed in both HIV/AIDS patients as well as in transplant recipients (73). Although incidence of cancer of the lower lip is increased in both populations, the increase was more marked in the transplant-recipient group (73). A similar pattern is observed in nonmelanoma skin cancer. While there is no known connection between lip cancer in renal transplant recipients and HPV or other viral infections, the risk factors were found to be related to exposure to UV radiation and tobacco products (74,75).

IV. MOLECULAR BIOLOGY AND GENETICS OF ORAL CANCER

Oral SCC, like many other epithelial cancers, evolves through the accumulation of multiple genetic and epigenetic alterations in a multistep process (7,76). Genetic changes commonly involved in oral cancer include loss of heterozygosity (LOH) at the sites of known or suspected tumor suppressor genes, mutation, and de novo promoter methylation of tumor suppressor genes, amplification or overexpression of oncogenes, and alterations in expression of DNA repair genes. Common LOHs are observed at 3p, 9p, and 17p. The deletion of two genes located on the short arm of chromosome 3; FHIT tumor suppressor gene and retinoic acid receptor (RAR)- β may play a role in development of oral cancer (77). P16INK4a (p16), which is a tumor suppressor gene and a member of the retinoblastoma pathway, is located at 9p21. High frequencies of deletions and mutations affecting this gene are observed in oral SCC (77,78). p16 is also subject to epigenetic control through hypermethylation of its promoter. TP53 (p53), a tumor suppressor gene located on the short arm of chromosome 17, is mutated in the majority of oral cancers and is also frequently deleted (58,77). Gene amplification and protein overexpression have also been found in head and neck carcinomas. Of special significance is epidermal growth factor receptor (EGFR), which has been targeted as a treatment strategy for oral SCC. Cyclin D₁ and p63 are other genes that are amplified (79,80). Overexpression of cyclooxygenase-2 (COX-2) is important in carcinogenesis and may provide molecular target for treatment (81).

Increased susceptibility to oral cancer is associated with a number of inherited cancer syndromes, including Li-Fraumeni syndrome, Fanconi’s anemia, and xeroderma pigmentosum (82). Polymorphism in genes involved in the metabolism of carcinogens contained in tobacco and alcohol have been linked to individual susceptibility. These genes encode for such enzymes as the glutathione-S-transferase, which are involved in detoxifying some carcinogens in tobacco. Other enzymes that metabolize carcinogens have also been implicated in oral cancer such as cytochrome p450, N-acetyltransferase and alcohol dehydrogenase (77,83). There is increasing evidence for an inherited genetic component in oral cancer, possibly associated

with a greater susceptibility to genetic damage by environmental mutagens. Those individuals may be more likely to develop multiple tumors (81,84).

A. Molecular biology in HPV-Related Carcinomas

Molecular changes in HPV-related carcinomas may differ from those induced by other carcinogens. A large body of studies in cervical, as well as HIV-positive oropharyngeal carcinomas, shows that HPV oncogenes E6 and E7 act through inactivation of P53 and retinoblastoma tumor suppressor genes, respectively. In addition, E6 can directly activate telomerase, and E7 induces abnormal centrosome duplication. Consequent cell cycle deregulation and genomic instability are instrumental factors for the developments of these distinct carcinomas, see *infra* (Fig. 35) (85–88).

V. CLINICOPATHOLOGIC CONSIDERATION

As stated above, SCC of the oral/pharyngeal mucosa constitutes a range of variants. Differences between these entities are not only morphologic but also clinical and in some cases molecular. The clinical and pathologic features of the following variants of SCC will be considered in some detail later in this chapter:

1. KSCC
2. Nonkeratinizing carcinoma
3. BSC
4. ASC
5. Adenoid squamous carcinoma
6. VC
7. Papillary squamous carcinoma
8. Spindle cell carcinoma (SpCC) (sarcomatoid carcinoma)

Staging of Oral/Pharyngeal Carcinoma:

Regardless of morphologic type, all variants of SCC are staged similarly using the TNM system (Table 1 and 2).

VI. KERATINIZING SQUAMOUS CELL CARCINOMA

KSCC is the prototype of SCC and is its most common type. It may occur at any of the anatomic sites of the oral cavity and oropharynx. Variations in clinical presentation, symptomatology, treatment outcome, and prognosis may to some extent depend on the anatomic location of the tumors. Because of such variations, the clinical aspects of carcinomas at various sites will be addressed separately.

A. Pathologic Features

KSCC bears some resemblance to keratinizing stratified squamous epithelium. The similarities vary depending on the degree of differentiation. Microscopically, KSCC is composed of sheets, strands, and nests of squamous cells. The tumor cells show abundant eosinophilic cytoplasm, well-defined cell

borders, intercellular bridges, and hyperchromatic nuclei. Varying degrees of nuclear and cellular pleomorphism are seen. A characteristic feature of KSCC is formation of keratin pearls (round cellular nests with central keratinization). Traditionally KSCC is graded as well, moderate, and poorly differentiated variants. Previously, the grading system, which was proposed by Broder (90), was based on the amount of keratin production and pleomorphism of the tumor cells. Four grades are described, grade I being the most differentiated with the highest keratin production and minimal cellular pleomorphism (Fig. 5), while grade IV is poorly differentiated with little or no keratin formation and marked cellular pleomorphism (Fig. 6). Grades II and III have intermediate levels of these characteristics (Fig. 7). The purpose of tumor grading is to provide a tool for predicting its biologic behavior. However, because the histologic features may vary considerably from area to area within the same tumor, the Broders grading system was found to lack significant prognostic value (91). Several authors suggested that more useful prognostic information may be deduced from the invasive fronts of the tumor where the deepest and presumably most aggressive cells reside (91–94). An invasive front grading system has been devised in which five histologic features are graded and assigned points from one to four. The score for each variant is summed to provide a total malignancy score for each tumor. The parameters used are degree of keratinization, nuclear pleomorphism, number of mitoses per high-power field, pattern of invasion, and host response. Accordingly, the lower score is given to tumors with high keratinization (>50% of cells), little nuclear pleomorphism, (>75% mature cells), 0–1 mitotic figures/HPF, pushing well-defined invasive front and marked host response. On the other hand, the highest scores are given to tumors with little or no keratinization, extreme nuclear pleomorphism, more than five mitoses/HPF, marked cellular dissociation in small nests or single cells, and no host response. The intermediate grade tumors have moderate levels of these features. This system has been found to be of high prognostic value for oral cavity carcinomas (91,92,95,96). This histologic grading of malignancy at deep tumor invasive front was also found to have significant positive relationship with Ki-67 cell proliferative index (97,98).

Other morphologic features that are found to have independent prognostic significance are presence of perineural invasion and intralymphatic tumor emboli (99–101). It has also been shown that the pattern of invasion, at the advancing front of the tumor, is a significant and independent predictor of both local recurrence and overall survival. The most unfavorable pattern is described as diffuse infiltration with cellular dissociation, while the most favorable is well defined with “pushing” border (118).

Many studies have advocated the use of tumor thickness as a measurable prognostic indicator in small tumors (T₁–T₂) (101–104). Tumor thickness was found to be significant in predicting local recurrence, nodal metastasis, and survival. However, a “cut off” thickness level that can be used to discriminate

Table 1 TNM—Staging System for Oral Cavity Cancer

Definition of TNM			
Primary tumor (T)			
TX		Primary tumor cannot be assessed	
T0		No evidence of primary tumor	
Tis		Carcinoma in situ	
T1		Tumor 2 cm or less in greatest dimension	
T2		Tumor more than 2 cm but not more than 4 cm in greatest dimension	
T3		Tumor more than 4 cm in greatest dimension	
T4 (lip)		Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose	
T4a		Tumor invades adjacent structures [e.g., through cortical (oral cavity) bone, into deep muscles of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, skin of face]	
T4b		Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery	
Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.			
Regional lymph nodes (N)			
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension	
N2		Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	
N2a		Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension	
N2b		Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	
N2c		Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	
N3		Metastasis in a lymph node more than 6 cm in greatest dimension	
Distant metastasis (M)			
MX		Distant metastasis cannot be assessed	
M0		No distant metastasis	
M1		Distant metastasis	
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Source: From Ref. 89.

between favorable and unfavorable prognosis has varied from 1.5 to 6 mm in various studies (102–106). The variation in results reported in these studies might be related to several factors, such as using the surface of the tumor or the adjacent normal mucosa as the point for measuring the thickness. More likely, the

variations were related to the size and peculiarity of the tumors. Studies on FOM and OT tumors showed cutoff thicknesses of 1.5 and 2.0 mm, respectively (107,108), while in the case of buccal mucosal carcinomas with marked keratinization, the prognosis was significantly worse for thicker tumors of more than or

Table 2 TNM Staging System for Oropharyngeal Cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor 2 cm or less in greatest dimension		
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension		
T3	Tumor more than 4 cm in greatest dimension		
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible		
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in lymph node more than 6 cm in greatest dimension		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping: Oropharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Source: From Ref. 89.

equal to 6 mm in thickness (106). In a study of 145 cases of oral carcinomas of all sites, O'Brian et al. (102) found that a 4-mm cutoff for good and poor prognosis applied to all sites.

KSCC is the most common type of oral/pharyngeal carcinoma of all anatomic subsites. Clinical presentation and etiologic factors may vary according to anatomic locations.

VII. SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

A. Squamous Cell Carcinoma of the Lip

As stated above, chronic exposure to sunlight is the most important etiologic factor. Lip cancer is more common in individuals who live in rural areas and

who are involved in outdoor occupations, particularly those with ruddy or fair complexions. It is also more prevalent in the Caucasian populations that live near the equator and is rare in blacks and dark-skinned persons (44,45,109–112). The incidence of carcinoma of the lip varies from 24% to 30% of oral cancers (113–115) and 12% of head and neck cancers (114,115). The lower lip is involved in 85% to 98% of cases (45,112,114,116,117) with a male predominance. The male-to-female ratio varies considerably in different series from 2:1 to 45:1 (45,113,116–118). The patients' age ranges from the fifth through the eighth decades of life (110,116,117,119–121) with a mean age of between 60.5 and 70 years (113,116,117,119–121).

SCC of the upper lip accounts for 1.8% to 7.7% of all lip cancers (122,123). Upper lip carcinoma is seen more frequently in women than in men (121,124). The

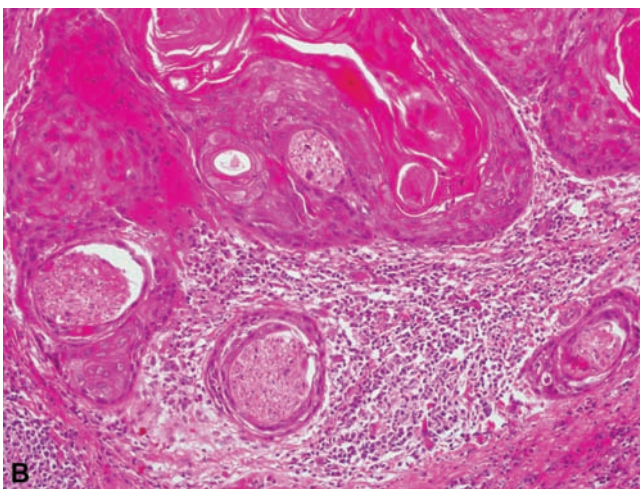
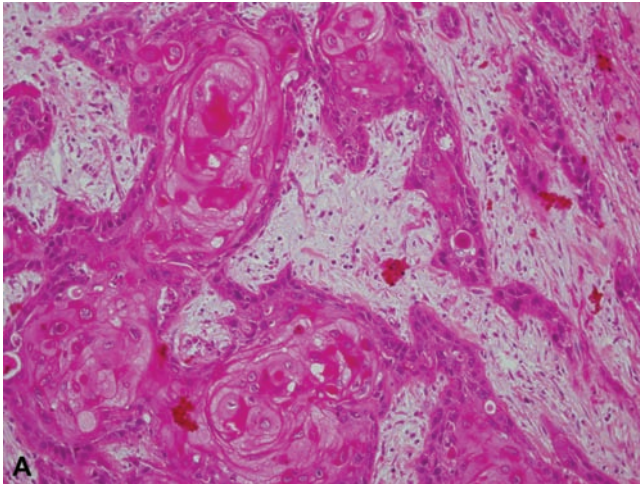


Figure 5 Well differentiated, KSCC (100 $\times$). *Abbreviation:* KSCC, keratinizing squamous cell carcinoma.

relative overall paucity of lip cancer in women has been attributed to the use of lipstick and less outdoor exposure, both of which make women less susceptible to the cumulative effects of actinic damage (124). Lip cancer is also virtually unknown in blacks and people with dark complexions (110). This apparent immunity is presumably due to the protective effects of melanin pigmentation against UV light (41,125).

Typically, carcinoma of the lower lip occurs at the vermillion border at a point midway between the midline and commissure area (1,23,126). Clinical presentations of the carcinomas vary considerably. Early lesions may be focal, white, and thick, diffuse mixed erythematous and white, have areas of chapping and crusting or fissures that do not heal. More advanced lesions may present as exophytic, infiltrating masses but more commonly as an ulcer (1,125–128) (Fig. 8). Palpable induration around the area of the lesion is an important diagnostic feature in all forms of the tumor (126,128).

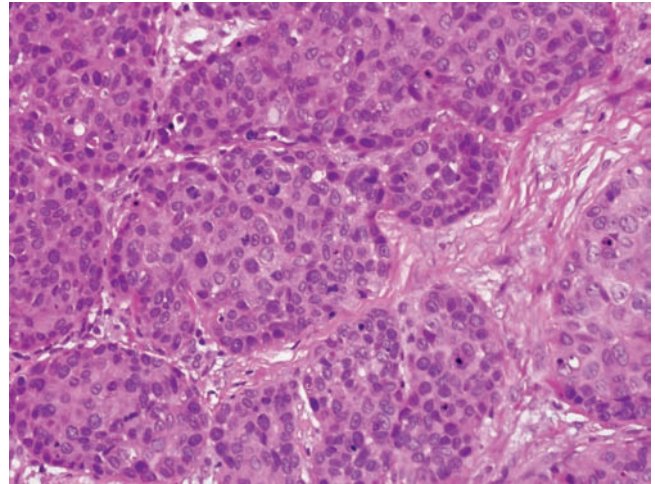


Figure 6 Poorly differentiated SCC. Although no keratin identified, the cells show keratinocytic phenotype (200 $\times$). *Abbreviation:* SCC, squamous cell carcinoma.

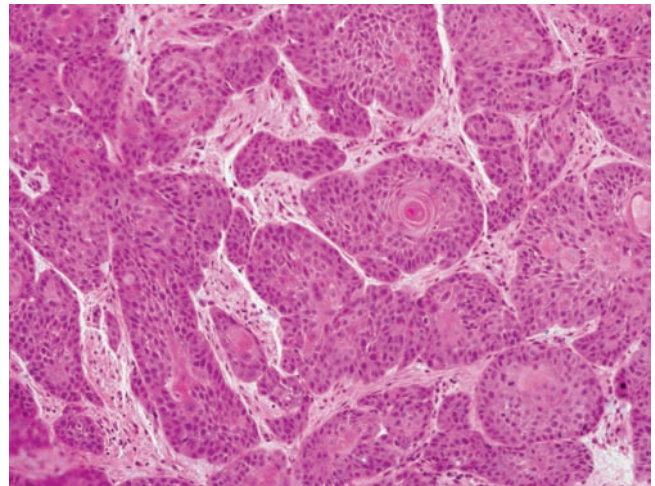


Figure 7 Moderately differentiated KSCC (100 $\times$). *Abbreviation:* KSCC, keratinizing squamous cell carcinoma.

Carcinomas of the lower lip, unlike that of the upper lip, tend to grow slowly. A considerable amount of time may elapse before a diagnosis is made (127). If untreated, the tumor may extend to contiguous structures such as skin, muscles, oral mucosa, and bone. Some carcinomas have a propensity for involvement of nerves. These may be associated with numbness of the lip. Involvement of the mental nerve may be limited, but on occasions, proximal extension of the malignant cells may follow the course of the inferior alveolar nerve within the mandibular canal and even along the mandibular branch of the trigeminal nerve through the foramen ovale and eventually intracranially. Such neurotropic behavior may be observed even when



Figure 8 SCC of the lower lip presenting as an ulcer. *Abbreviation:* SCC, squamous cell carcinoma.

other risk factors, such as tumor grade and stage, are favorable (129–134). The mechanisms involved in neurotropic behavior of some SCCs are currently unknown. Neural involvement in lip carcinoma can be determined clinically by sensory complaints such as burning, stinging pain, or numbness along the course of the affected nerve and by radiographic findings of widening of the osseous canals or erosion of skull foramina with which the affected nerves are associated (129). Lymph node metastases from carcinoma of the lower lip develop late in the course of the disease. It is identified in 12% or fewer of the cases (116,117,121,122,124,127). The submental and submandibular lymph nodes (levels Ia and b) are most commonly involved. Contralateral metastasis occurs when the tumor is near the midline, because of cross-drainage of lymphatics present in this location. The size of the tumor is an important risk factor for lymph node metastasis. Carcinomas that are smaller than 2 cm rarely metastasize, whereas those that are larger disseminate to lymph nodes with the same frequency as carcinomas of the FOM and tongue (126). In one study, only 5% of T₁ and T₂ lesions demonstrated nodal metastasis. In contrast, 67% of T₃ and T₄ carcinomas spread to the cervical lymph nodes (135). In another series, 7% of 757 patients with T₁ cancer demonstrated cervical metastasis as compared with 16% of 249 of patients with T₂ to T₄ tumors (124).

Distant metastasis from lip carcinoma is quite rare. In a review of 845 cases, systemic spread was noted in 1.6% of the cases. The lung, liver, heart, and spleen were the sites most frequently involved (136).

Treatment and Prognosis

Surgery and/or radiation therapy are used with good results in managing smaller tumors of the lower lip, both achieving equally high local control rates of more than 90% (122,137–139).

Radiotherapy is contraindicated in the following conditions: young patients, recurrence following initial radiation therapy, large tumors with possible neural involvement, and where there is extensive

solar keratosis affecting the rest of the vermillion border (140).

Surgical management of smaller lesions is usually in the form of a wedge or V-shaped resection with primary closures. Larger defects require reconstructive procedures. Lip shave and vermillionectomy, in addition to the simple resection, are recommended in patients with demonstrable premalignant actinic changes (117,141). Cases in which tumor involves the mental nerve, efforts are made to prevent the progression of cancer cells along the inferior alveolar nerve back to the base of the skull. This may involve a hemimandibulectomy or, if possible, unroofing of the nerve in the inferior alveolar canal and resecting it with a free proximal margin (129). In such cases, surgery is followed by radiation therapy (142,143).

Routine elective node dissection in patients with clinically negative neck has been largely abandoned because of low yield of nodal metastasis. A cure rate of 90% is reported in T₁ to T₂, N0 carcinomas of the lower lip (47,116,117,119). However, supraomohyoid neck dissection is advocated in large T₃ and T₄ tumors, clinically positive nodes, and carcinomas at the oral commissure (144).

Neck dissection combined with postoperative irradiation has been highly successful in regional control (138,141). Cases in which lymph node metastasis is pathologically proven, the average five-year survival rate is estimated to be 50% (47,116,119, 120,122,124).

Frierson and Cooper developed a cytologic grading system for lip cancer similar to the grading system of the advancing front alluded to above. Four grades are described, which have prognostic implications. They show a three-year cure rate of 95% for grade I lip tumors but only 46% and 38% for grades II and III, respectively (120).

B. Squamous Cell Carcinoma of the Buccal Mucosa

Many of the etiologic factors described above have been implicated in the causation of cancer of the buccal mucosa, in particular, tobacco habits, both smoked and nonsmoked, and alcohol abuse. The incidence of SCC of the buccal mucosa varies in different reports from 1% to 10% of oral/oropharyngeal carcinoma (145–147).

In India, where betel nut and other chewing habits are prevalent, it constitutes 44% of all SCC of the oral cavity (148). In a recent study from India of 100 cases of carcinomas of the buccal mucosa, 95% of the patients gave a history of abuse of oral tobacco products (149).

Most cases occur in the sixth and seventh decades of life (147,150,151). The male-to-female ratio ranges from 2:1 to 9:1 in most investigations (145,149,150,152). However, in southeastern and southwestern United States, carcinoma of the buccal mucosa has occurred as often, if not more frequently, in women. This has been attributed to the excessive use of snuff and chewing tobacco by females in those areas (22,153). Early SCC of the buccal mucosa may

present as a white plaque (leukoplakia), red plaque or macule (erythroplakia) (Fig. 9), or exophytic verrucous hyperplasia (VH). The advanced lesions may appear as a fungating mass with a granular red surface or as ulcerating infiltrative cancer (Fig. 10). Marked infiltration of the lamina propria and into the underlying buccinator muscle and buccal fat is a characteristic feature even in small T₁ lesions (153,154). VC commonly occurs in the buccal mucosa and is discussed independently later in this chapter.

The signs and symptoms of the disease are dependent on the degree to which the cancer has progressed. Early lesions tend to be asymptomatic but eventually “soreness” becomes the most prominent initial complaint. As the tumor enlarges, trauma, superimposed infection, and swelling result in increased pain. Involvement of the masticator spaces in the process may lead to trismus. The tumor may slough and form a foul-smelling mass in the mouth or may ulcerate and appear externally on the skin. Hemorrhage from the internal maxillary or facial arteries is



Figure 9 SCC of the buccal mucosa presenting as erythroplakia with leukoplakic areas. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 10 SCC of the buccal mucosa presenting as an exophytic mass. *Abbreviation:* SCC, squamous cell carcinoma.

a potential complication. Paralysis of branches of the facial nerve may also occur (155,156). Invasion of the mandible or maxilla may be present in advanced cases. Death occurs from combination of infection, malnutrition, and hemorrhage.

Treatment and Prognosis

Primary radiation therapy is a good therapeutic option for early buccal carcinoma (154,155,157). Patients with larger tumors show higher rates of recurrence. Wide local resection even in small T₁ to T₂ tumors is associated with high recurrence rates (154,157), while aggressive composite resection has better results (157). An improvement of the determinate cure rate from 28% to 42%, when surgery replaced radiation therapy as the preferred treatment, was reported in a study from Memorial Sloan-Kettering Cancer Center (145). In this study the presence or absence of nodal enlargement was the most significant prognostic factor. Patients treated surgically for residual or recurrent buccal carcinoma have extremely poor prognosis (155). The question of whether or not to use surgery or irradiation to manage the neck with clinically negative nodes has not been resolved. It is suggested that prophylactic intervention is unwarranted because of the low yield of occult nodal metastasis (157,158).

Chemotherapeutic treatment of buccal carcinoma using a variety of agents has not been very promising. Use in larger tumors, T₃ to T₄, resulted in some tumor regression in a minority of cases (155,159–161). The vast majority needed surgical salvage, and nodal regression was not significant in any case.

Regardless of the type of treatment, locoregional recurrences are common, usually occurring within 18 months (155,161,162). Several factors affect the prognosis: tumor size, location, and thickness as well as presence or absence of nodal metastasis. Carcinomas located anteriorly near the commissure area have more favorable prognosis than those present posteriorly. The latter have a tendency to invade the oropharynx and bone of the mandible and maxilla (163). Tumor size is useful in predicting outcome only at the extremes; (T₁ and T₄), but that discrimination is lost in the intermediate sizes T₂ and T₃ (106). Tumor thickness is suggested as a significant independent variable in prognosis. The cutoff thickness for buccal cancer is believed to be 6 mm, with five-year survival rates significantly better for tumors less than 6-mm thick. Patients presenting with cervical lymph node metastasis are found to have a five-year cure rate of only 23% compared with 56% for those patients without nodal disease (164).

C. Squamous Cell Carcinoma of the Floor of the Mouth and Oral Tongue

The FOM and the anterior two-thirds of the tongue (OT) are the most common sites of oral SCC. They account for more than 60% of all oral carcinomas excluding the lips (165). The frequency of carcinoma of the OT exceeds that of the FOM (165–167). In a

review of 58,976 cases of oral cancer extracted from the National Cancer Database (NCDB), the OT accounted for 31.9% and the FOM 28.4% of the cases. These tumors demonstrate locally aggressive behavior related to lack of anatomic barriers to spread and a propensity for cervical metastasis (168).

Etiology

Excessive smoking and alcohol abuse are the main etiologic factors. Prolonged contact of the potential carcinogens in the salivary reservoir with FOM and OT mucosa may play a role in targeting these sites specifically (169). These usual risk factors are not always apparent, particularly in cases of OT cancer in patients younger than 40 years. In this population, other risk factors may be involved, particularly genetic predisposition (170–172). Many younger patients with tongue cancer have never smoked or consumed alcohol, and in any case, the exposure to those carcinogens might be of too short duration for malignant transformation to occur (172,173).

Clinical Features

Carcinoma of the OT and FOM are predominantly diseases of the elderly with the greatest majority of cases occurring in the sixth to the eighth decades of life with a median age of about 60 years (165,169, 174,175). A small minority of cases occur in young patients in the second and third decades of life. It has been estimated that about 3% of carcinomas of the OT occur in young patients but an increase to 6% to 7% has been recently recognized (176–178). In the United States, the incidence of OT cancer has increased in adults aged 20 to 44 years during the last three decades (177).

In general, men are affected two to three times as much as women. However, the gap appears to be closing during the last several decades in various parts of the world. The difference seen previously was probably a reflection of the differences in habits between males and females. As habits such as smoking and drinking became more socially acceptable among women, the gap has narrowed (166,172,179–182). Among young patients with OT cancer, it is particularly noticeable that the proportion of women is greater than in the general population of tongue malignancies, yet a history of smoking and drinking is less frequently reported (183–187) (Fig. 11). Tongue carcinoma in patients younger than 40 years may be a distinct biologic entity but as alluded to above, the underlying causes remain unknown (170–172).

Early asymptomatic carcinomas clinically present as either leukoplakia or, more commonly, erythroplakia (Fig. 12). Shafer and Waldron found that 50% of erythroplakia of the FOM were histologically proven to be invasive carcinoma. The remainder were either severe dysplasia or carcinoma in situ (188). However, the typical patient presents with a painless, indurated ulcer of several months' duration (Fig. 13). The lesions are frequently more than 2 cm in diameter at the time when the true nature of the



Figure 11 SCC of the tongue in a 19-year-old woman with no history of smoking or excessive drinking. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 12 Early SCC of the tongue seen as an area of erythroplakia on the lateral border. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 13 Typical SCC of the lateral border of the tongue presenting as a painless indurated ulcer. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 14 SCC of the anterior FOM near the lingual frenulum. Abbreviations: SCC, squamous cell carcinoma; FOM, floor of the mouth.

disease is established (188–191). In cases of FOM tumors, the most common site is anteriorly, near the lingual frenulum (Fig. 14). Seventy-two percent of all tumors occur in this location, whereas 15% to 30% develop in the middle third and posterior third, respectively (189,191–193). However, restriction of the tumor to the confines of the FOM is generally found only in the initial stages of the disease. Extension to contiguous structures occur in 50% to 70% of the cases at the time of diagnosis (194–196). In the case of the OT, the most common site is the lateral border of the middle third. About 75% of all tumors occur in the lateral border followed, in descending order, by the ventral surface, dorsum, and the tip.

The ulcerated lesions are often only the “tip of the iceberg.” Manual palpation helps in appreciating the third dimension of the lesion. Some tumors have exophytic components. More advanced carcinomas are symptomatic. The patients may experience feelings of discomfort, pain, excessive salivation, or hemorrhage. Tongue involvement produces some limitation of movement, resulting in slurred or difficulty in speech. Involvement of the base of the tongue may lead to dysphagia and referred otalgia (188,197,198). Weight loss is reported by one-third of the patients (198). At the time of diagnosis, the majority of OT and FOM tumors are classified as T₁ and T₂ (54–67%) (175,198–201). The percent of patients presenting with clinically positive cervical lymph node metastasis varies from 30% to 63% (174,175,198,200,202,203). In general, the nodes most commonly involved are those of the submandibular and upper jugular (levels I and II). Dissemination to lymph nodes of levels III, IV, and V occur less often (195,204,205). Anterior lateral and midline lesions have a propensity for contralateral nodal involvement (206). The orderly progression of metastasis from upper to lower lymph nodes is not always apparent; skip metastases are common. Although some studies have found a positive correlation between tumor size and metastatic potential (206), others have found that T stage is of little predictive value (101,207,208). On the other hand, as mentioned before, tumor thickness has been advocated as a significant predictor of lymph node

metastasis (101–104,107,108,208). In any case, most of the patients have stages III or IV disease at presentation (181,209).

Distant metastases are unusual, occurring only in 10% of the patients, with the lungs, liver, and bone as the sites most commonly affected (181,190,192,205). Secondary primary carcinomas are known to be associated with FOM and OT carcinomas in 4% to 54% of the cases. The secondary primary carcinomas may be synchronous or asynchronous and occur mostly in the head and neck area (181,189,192,194,205,207,210–212). Half of these second primaries are detected by two years from the index tumor presentation, but non-aerodigestive tract tumors are common beyond five years (213).

Treatment and Prognosis

Surgery and radiation, either alone or in combination, are the prime modalities used in the treatments of carcinomas of the OT and FOM. Chemotherapy has been used as initial treatment concurrently with radiotherapy or as adjuvant treatment following surgery or irradiation. For the most part, early carcinomas (stages I and II) are treated effectively with either surgery or radiotherapy alone (174,175,181,200,205).

Involvement of the mandible by carcinoma is an important consideration in selecting appropriate therapy. Assessment of bone involvement by tumor may be done by clinical examination and radiographic studies. Plain radiographs may be helpful in judging the gross extent of mandibular invasion, but they are of little or no help in determining early or minimal intraosseous invasion (214–216). Computed tomography (CT) scans provide good cortical bone detail. Magnetic resonance imaging (MRI) is generally more reliable in detecting changes within the marrow cavity. Both of the foregoing procedures have produced false-negative and false-positive results as well as under- or overestimation of the depth and width of the invasion (214,217,218). The concomitant use of both MRI and CT scans has been suggested (219).

If the mandibular bone is minimally involved, a marginal resection (excision of the alveolar process above the mandibular canal) is considered. In patients with clearly demonstrable clinical or radiographic evidence of mandibular invasion, a segmental mandibulectomy is needed with a 1 to 2 cm resection margin (190,195,196,215) (Fig. 15). Tumors that extensively invade bones are usually less amenable to cure by irradiation alone and are complicated by high incidence of osteoradionecrosis.

Treatment of the neck is recommended in patients with clinically positive cervical lymph nodes at presentation. For N1 metastasis, neck dissection alone is appropriate. For more advanced neck metastasis, a neck dissection with or without radiotherapy is needed (220). On the other hand, the question of treatment of the clinically negative neck is controversial. Recommendations for management of the negative neck in stages I and II disease have included observation alone or prophylactic neck dissection and prophylactic irradiation. On the other hand, there is

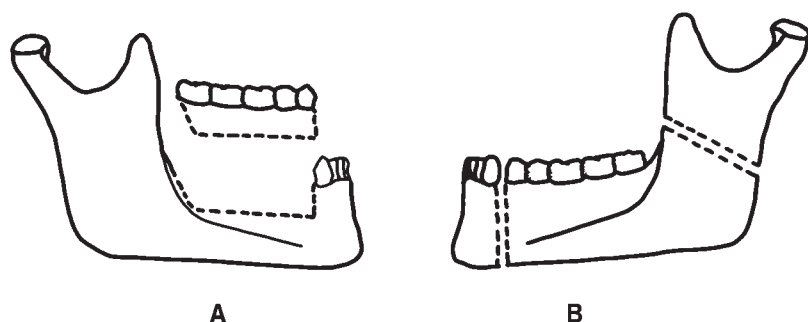


Figure 15 Diagrams illustrating (A) marginal and (B) segmental mandibulectomy.

general agreement on the need to treat the neck in all T₃ and T₄ tumors (180,181,220–223). Other considerations that are taken into account in deciding whether or not to treat the neck prophylactically in cases of T₁ and T₂ tumors include depth and pattern of invasion, lymph vascular involvement, perineural invasion, and patients who are not amenable to follow-up.

The most common causes of treatment failure are the usual events: large tumors, tumor thickness, positive margins of excision, perineural invasion, infiltrating pattern of the advancing front, lymph node metastasis, extranodal spread of tumor, and distant metastasis (95,118,224–229). The incidence of local recurrence following surgery or irradiation varies from 10% to 40%. Over 90% of the patients who fail therapy, regardless of the modality employed, will manifest local or regional recurrence within two years (181,189,190).

Several reports of large series of cases have emphasized the importance of early detection for more favorable prognosis. Figures based on clinical stage of the tumors have shown a five-year survival rate of 69% to 90% in stage I disease and 0% to 26% for stage IV disease (165,174,181,190,192,194–196,200,230–232). As previously mentioned, some investigators have found that young patients, less than 40 years of age, with OT cancer tend to have poorer prognosis (171,172,176,178, 183–185,187,233) even when presenting with early-stage disease, with a locoregional recurrence of 57% and death caused by disease in 47% of the cases (234). It was therefore recommended that an aggressive therapeutic approach be taken in young patients with carcinoma of the anterior two-thirds of the tongue.

Distant metastasis, usually to the lung and bone, is estimated to occur in 5% to 15% of the cases, and of these, 90% expire within two years. Larger estimates of distant metastasis below the clavicles are reported on the basis of autopsy studies (228,235–239). About 20% to 30% of patients will develop a second primary malignancy during the course of their disease (220,228,240).

D. Squamous Cell Carcinoma of the Gingiva and Alveolar Mucosa

The gingiva is the part of the oral mucosa that covers the alveolar process of the dentate jaws. Mucosal

covering of the mandibular and maxillary ridges in edentulous areas is the alveolar mucosa. For the purpose of the current discussion, both the gingival and alveolar mucosa will be referred to as gingival mucosa. Gingival SCC is the third most common intraoral carcinoma after cancers of the tongue and FOM. It constitutes 4% to 25% of all oral cancers (166,167,241–248).

Of particular significance is that gingival SCCs may clinically simulate inflammatory gum diseases such as chronic gingivitis, periodontal disease, and periodontal abscess. Consequently, misdiagnosis and delayed diagnosis are not uncommon (241,248–251). In addition, gingival carcinoma is characterized by early, and sometimes extensive, involvement of underlying bone with impending poor outcome (250–256).

Etiology

Several investigators have indicated that tobacco use and, in particular, snuff dipping is a major risk factor in the etiology of gingival carcinoma (22,241,245,257,258). Alcohol consumption (246,259) and poor oral hygiene (245,258) are also important considerations. Other studies, on the other hand, have suggested that the risk of alcohol and tobacco usage is not as significant for gingival carcinoma when compared with that of the tongue and FOM tumors (12,166,259–261).

The occurrence of gingival SCC in young patients with HIV/AIDS and in patients with graft-versus-host disease following marrow transplants, in the absence of the usual risk factors, suggests an etiologic role for immune disorders (262–264). A genetic bases for gingival carcinoma is postulated on the basis of the detection of p53 mutations and overexpression in many cases (58,77,265). The high incidence of gingival SCC in patients with proliferative verrucous leukoplakia (PVL) (266) may also suggest a genetic basis (see *infra*).

Clinical Features

Gingival carcinoma is primarily a disease of the elderly, with the vast majority of cases occurring in individuals of 50 years or older (241,246,267,268). Only a few cases of gingival carcinoma have been reported in patients younger than 40 years, (269,270) including one adolescent patient (271). Data derived from several

earlier series indicated that this disease usually involves the mandibular gingival and affects men more often than women (147,167,241,245–247,268,269,272). However, more recent findings have shown a decrease in the male-to-female ratio and even a reversal in gender presentation (166,243,267,273,274).

Gingival carcinoma can present as an area of erythema, an ulcer, or an exophytic mass, resembling hyperplastic granulation tissue and mimicking focal inflammatory gingival hyperplasia (188,275–277). The carcinoma is more prevalent posterior to the canine area, most commonly the mandibular molar area (278,279). Quite often the lesion is asymptomatic (246,278). More advanced cases may present with soreness and pain of the gingiva, toothache, or bleeding (246,278,280). Typically, this cancer extends along the periodontal membrane with destruction of the supporting bone, resulting in loosening of the teeth, closely resembling advanced periodontal disease (242,277) (Fig. 16). Consequently, it is not unusual for the involved teeth to be extracted, and the true nature of the disease becomes apparent when the tooth sockets and surrounding tissue fail to heal (241,242,246,278). On the alveolar ridge, the carcinoma often grows in the form of a flat elongated ulcer (281). The duration of the symptoms in 187 patients, analyzed by Soo et al. (246), varied from three to more than six months.

The tumors may spread laterally to involve the mucobuccal folds, cheek, and lower lip (Fig. 16) or medially leading to invasion of the hard palate, FOM, and ventral surface of the tongue (278,282). Involvement of the mandibular or maxillary mucobuccal fold in edentulous patients who wear dentures may give rise to a mass that lies in close proximity to the flange of the denture. The clinical appearance of these lesions may be identical to inflammatory fibrous hyperplasia (epulis fissuratum) (279) (Fig. 17).

Because of its proximity to alveolar bone, gingival carcinoma commonly shows evidence of bone invasion (Fig. 18). Bone is usually involved early in the course of the disease. Clinical and radiographic



Figure 16 Gingival SCC in the maxillary molar area extending into the buccal mucosa. Notice destruction of the periodontium and resemblance to advanced periodontal disease. *Abbreviation:* SCC, squamous cell carcinoma.

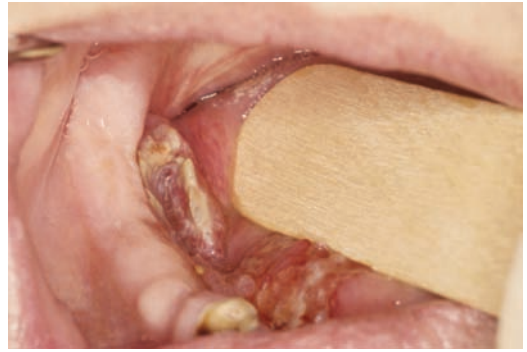


Figure 17 SCC of the lingual alveolar mucosa of edentulous mandibular ridge, resembling inflammatory fibrous hyperplasia. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 18 Dental radiograph showing bone destruction at the site of gingival SCC in the mandibular molar area. *Abbreviation:* SCC, squamous cell carcinoma.

evidence of osseous invasion has been noted in up to 75% of patients (246,253,255,256,283,284). This process does not appear to correlate with the site of the lesion or the stage of the disease but is dependent on the proximity to bone (284,285). Mandibular tumors may extend to the mandibular canal and the inferior alveolar nerve. Paresthesia of the lower lip may develop. In the maxilla, penetration of the antrum is a frequent occurrence (252,253,256,278).

Metastasis to cervical lymph nodes may be influenced by the location of the tumor and the T stage of the disease. Mandibular tumors metastasize more readily than maxillary ones. Clinically involved nodes were found in 30% to 32% of the patients with mandibular tumors and 9% to 14% in patients with maxillary carcinomas (246,286).

The relationship between cervical metastasis and tumor stage was investigated in 109 individuals. The incidence of nodal involvement was found to increase with the T stage of the disease (246). Dissemination to

distant sites developed most often in the presence of extensive cervical metastasis or in the presence of bone involvement (246).

Radiography

Although radiography generally provides relatively reliable indication of bony involvement (Fig. 18), the absence of detectable changes does not completely exclude the possibility of invasion. Microscopic evidence of bone invasion is frequently seen in spite of radiographic findings (252,287). Additional techniques, other than intraoral and extra oral plain film radiography, are usually needed. CT scans, MRI, and bone scans are all used for ascertaining bone involvement (252,253,256). CT scans are the most frequently used and are usually the only necessary radiologic examination. CT can usually predict areas of bone invasion with a degree of accuracy (254). MRI has an advantage in demonstrating malignancy in the bone marrow and perineural sheath. MRI can also aid in delineating fluid from soft tissue when the paranasal sinuses are involved (254). Severe bone destruction may result in displacement of teeth and their isolation producing "floating teeth" effect and may induce pathologic fractures (288).

Treatment and Prognosis

Surgery is the mainstay treatment of gingival carcinoma. Marginal mandibulectomy in appropriately selected cases is as effective as segmental jaw resection (246,289-292), and maintenance of the mandibular continuity results in significant reduction in patient morbidity and good long-term functional results (246,291). Segmental jaw resection is reserved for cases in which bone destruction extends to the inferior alveolar canal on imaging examination (Fig. 15). Hemimandibulectomy is done in patients with unilateral involvement of the entire inferior alveolar canal (252,290,293,294).

Clinically positive cervical nodes N_1 to N_3 are treated with modified or radical neck dissection. For clinically N_0 necks, a supraomohyoid neck dissection is recommended (246,290). Postoperative radiotherapy is used in patients with cervical metastasis as well as in patients in whom tumor margins are inadequate or who have advanced stage disease (i.e., stages III and IV) (246,290,295). Chemotherapy has been used in advanced cases (249,295).

Several factors play a determinant role in the prognosis of gingival SCC. These include the size and site of the tumor, presence or absence of bone involvement and its extent, the adequacy of the surgical margins, and presence or absence of metastasis (241,245,269,291,296). Maxillary carcinomas have better outcomes than mandibular ones with five-year cures of 52% and 45%, respectively (22).

The main predictor of survival is considered to be the stage of the tumor at the time of diagnosis (246,253,256,280). Five-year survival rates decline from 55% to 75%, for stages I and II patients, to 24% to 44% in more advanced cases (246,280).

E. Squamous Cell Carcinoma of the Hard Palate

The hard palate is the rarest site of intraoral SCC. It is, however, the most common site for minor salivary gland adenocarcinoma of the mouth. As previously alluded to, SCC of the hard palate is rather common in some parts of India where reverse Chutta smoking is prevalent (1,15,297,298). The hard palate is, however, not uncommonly involved by extension of maxillary gingival and alveolar ridge SCC (253,256).

In the United States, the peak incidence of occurrence is between 60 and 70 years of age. Although some studies have found that it is more common in men, other studies have indicated that women are more often involved (299,300). The first sign of the disease is a lump or an ulcer (Fig. 19) that may or may not be painful but occasionally bleeds. Exophytic growths are most common and can result in denture malfunction in individuals who wear a maxillary prosthesis. Leukoplakia is detected in one-fourth of the patients in association with the tumor (301). The average delay from onset of symptoms to diagnosis has been as long as four to five months (299,302). The tumors are fairly well distributed between the two sides and the center of the palate (301). In reverse smokers, however, the cancer usually develops as an ulcer, lateral to the midline in the glandular zone of the hard palate (297).

At the time of diagnosis, about half of the tumors are localized to the hard palate, 30% have invaded adjacent structures, and 15% to 30% are associated with positive cervical lymph nodes, 5% of which are bilateral (299,300,302). Close to one-half of the tumors are less than 4 cm in diameter. From the hard palate, the cancer may spread to invade the underlying bone, floors of the maxillary sinus and nasal cavity, gingiva, and soft palate. Invasion through the bone and into the maxillary sinus or nasal cavity is usually a late event. The submandibular and subdiaphragmatic lymph nodes are the first to be involved with metastatic carcinoma (301,303). Distant metastases are rare.



Figure 19 Ulcerated, exophytic SCC of the hard palate in an edentulous patient. *Abbreviation:* SCC, squamous cell carcinoma.

Treatment and Prognosis

Some clinicians prefer surgery over radiotherapy as the prime therapeutic modality for SCC of the hard palate (254,302). Others, however, have found irradiation to be equally effective and without significant complications (299,304). Kovalic and Simpson (305) were able to achieve good 10-year local control and disease-free survival rates when surgery was combined with irradiation. The mean overall five-year determinant survival has ranged from 31% to 59% (300–302,306). For stages I to IV, the five-year survival rate was found to be 75%, 46%, 36%, and 11%, respectively (300), almost 80% of these patients who fail therapy do so within 18 months after treatment. Fifty-three percent of the treatment failure occurs in the primary site, 30% in the neck alone, 10% at both primary site and neck, and 7% at distant sites along with locoregional recurrence (300). Because of significant prevalence of cervical metastasis from cancer of the palate, it is recommended that selective elective neck dissection should be offered to the patients (307).

VIII. SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

As previously indicated, the oropharynx encompasses five anatomic areas: palatine tonsils, base of tongue, soft palate and uvula, oropharyngeal walls, and RMT. Although the latter is technically a component of the oral cavity, carcinomas of this area often involve adjacent sites of the oropharynx and behave more like oropharyngeal tumors and thus will be discussed in this section.

A. Squamous Cell Carcinoma of the RMT

The RMT is anatomically a part of the oral cavity rather than the oropharynx. It consists of a roughly triangular strip of mucosa that covers the ascending ramus of the mandible immediately posterior to the last molar tooth and ends at the apex of the tuberosity of the maxilla (Figs. 1, 4). Laterally it merges with the buccal mucosa, and medially it blends with the anterior tonsillar pillar, soft palate, and FOM. Anteriorly it is in contact with the mandibular gingiva and posteriorly relates to the muscles of mastication (pterygoid and masseter) and mandibular bone.

Tumors involving the RMT may be extensions from subjacent sites such as the buccal mucosa, FOM, posterior tongue, soft palate, or tonsils. These tumors are described under their respective sites. Carcinomas primarily of the RMT are relatively uncommon and will be discussed here. The tumors have been linked etiologically to tobacco and alcohol abuse (308,309).

Clinical Features

SCC of the RMT occurs primarily in men of 55 to 70 years of age (309–311). Tumors in this region are characterized by early invasion of the buccal mucosa, soft palate, and mandible (309,310) (Fig. 20). They are often diagnosed at an advanced stage owing to the



Figure 20 Ulcerated SCC of the RMT, involving the soft palate and mandible. *Abbreviations:* SCC, squamous cell carcinoma; RMT, retromolar trigone.

absence of early symptoms. The prognosis tends to be poor because of late stage at the time of presentation (308–310). Advanced disease is symptomatic, commonly associated with pain and trismus. The symptoms may result from invasion of the branches of the mandibular nerve and muscles of mastication. Referred otalgia is also common. At the time of diagnosis, 27% to 60% are associated with clinically positive lymph nodes, especially those of levels I and II (309–314). In one study of 31 patients with RMT carcinoma, occult metastasis was found in 64% of clinically N0 necks (308). Histologically documented invasion of the underlying mandibular bone was reported in 14% of the cases in one study and 50% in another (310,314). MRI was found to be more sensitive than CT scan in predicting infiltration of the mandibular marrow by tumor. The respective sensitivity was 100% and 50% (314,315).

Treatment and Prognosis

The optimal management of carcinoma of the RMT is not yet clearly determined. While some studies advocate surgical management, others recommend radiotherapy. However, it is generally agreed that small T₁ and T₂ lesions can usually be treated effectively with radiation or surgery (316–320). Wide excision is necessary even in the absence of bone invasion. When bone is involved, marginal or segmental mandibulectomy is required. Adequate surgical margins improve survival (309,316).

Huang et al. (321) in their review of 65 patients showed a five-year disease-free survival of 31% with radiation alone, compared with 90% and 63% with surgery and pre- or postoperative radiation, respectively. These authors recommended combined surgery and radiotherapy for all stages of disease. In another study, the five-year overall survival was 40% in patients managed with radiation alone and 56% managed with surgery and radiotherapy (322). Using multivariate analysis, they found that stage and treatment modality were significant predictors of

survival. Concurrent chemotherapy and radiation therapy are occasionally used for advanced stages, with some increase in survival rates (316). Distant metastasis eventually occurs in 8% to 18% of the patients (312,313). Lymph node status is reported to significantly influence disease-free survival and distant metastasis rate (321).

B. Squamous Cell Carcinoma of the Soft Palate and Uvula

The soft palate is an oropharyngeal structure. It is contiguous with the tonsillar pillars inferiorly and the hard palate anteriorly. It separates the nasopharynx from the oral cavity and oropharynx. It approximates the posterior pharyngeal wall during swallowing, to prevent nasopharyngeal regurgitation, and during speech, to prevent nasal escape of air.

Clinical Features

The soft palate represents 5% to 12% of all oropharyngeal carcinomas (323,324). Although the soft palate is not an uncommon site for malignant tumors of minor salivary gland, SCC is the most common malignancy (324). The majority of the lesions develop on the oral surface. Epidemiologically, these tumors are associated with tobacco and alcohol use. SCC of the soft palate and uvula is two-to-three times more abundant in men than women and in blacks more than whites and tends to occur in older individuals with an average age of about 60 years (323–329). Because of its abundant nerve supply, most patients (60–80%) present within three months of onset of symptoms and typically complain of a persistent sore throat, pain on swallowing, or referred otalgia (330,331). In a review of 188 cases of SCC of the soft palate and uvula, Weber et al. (329) observed that 80% were unilateral and 20% were either midline or bilateral. The uvula was the site of the primary in 2.7% of the cases (329). Approximately 30% to 35% of patients (range 23–50%) will have positive cervical lymph nodes at diagnosis, and of these, 3% to 13% may be bilateral, especially if the lesion approaches or crosses the midline (326,327, 329–333). The subdiaphragmatic and midjugular lymph nodes are most often involved.

As the tumor enlarges, it is not uncommon for it to spread beyond the soft palate to involve other sites, especially the tonsils, RMT, base of tongue, and pharyngeal wall. The lesions may present as an exophytic growth, an ulcer, a slightly elevated plaque, or as a diffuse area of erythroplakia (Figs. 21–23).

Treatment and Prognosis

The tumor can be treated either by irradiation, surgery, or both. In general, early well-localized lesions can be safely excised without causing significant functional disability, whereas more diffuse or poorly defined lesions are best treated with radiation. Advanced tumors associated with regional lymphadenopathy generally require a combination of both modalities.



Figure 21 Early SCC of the soft palate presenting as erythroplakia. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 22 Ulcerated SCC of the soft palate extending into the mucobuccal fold. *Abbreviation:* SCC, squamous cell carcinoma.



Figure 23 Exophytic SCC of the soft palate. *Abbreviation:* SCC, squamous cell carcinoma.

The five-year determinant survival ranges from 55% to 77% (325,327,329,330,332). Morse and Kerr (334) found significant disparities in survival between black males compared with white males. The difference in mortality rates for white and black females was small.

Local recurrence occurs in 25% to 37% of the cases, and second primary malignant tumors are not uncommon (24–42% of the cases) (325,326,328–332). The incidence of distant metastasis during the course of the disease has varied from 0% to 22%. Most of these are to either bones or lungs. It has been pointed out that despite combined modality therapy with surgery and radiation, the five-year survival for stages III and IVa resectable tumors is poor (33–47%) (329,331,335–337). It has been recently shown that the reason for the poor outcome in those patients relates to occult metastatic disease in the parapharyngeal space (324). The parapharyngeal space is outside the surgical boundaries of a peroral resection and neck dissection. Furthermore, the risk of transverse myelitis limits the amount of adjuvant radiation that can be given to this area, in a standard opposing field anterior-posterior technique (324).

The use of neoadjuvant chemoradiation offers another therapeutic regimen that may be of benefit in advanced stage disease (338). Intensity-modulated radiation therapy (IMRT) may provide higher doses to and better control of the occult metastatic disease in the parapharyngeal space without the risk of transverse myelitis (324).

C. Squamous Cell Carcinoma of the Oropharyngeal Wall

The posterior and lateral walls of the oro- and hypopharynx are anatomically and functionally one structure. Tumors in this location have similar risk factors, lymphatic drainage, clinical behavior, and prognosis and are normally treated in the same manner (339–346).

Clinical Features

Tumors of the oropharyngeal walls are relatively rare. They are more common in males and affect patients with a median age of 60 to 65 years (339,342,345–349). Tumors at this site are usually quite large when first seen. They tend to have a pattern of submucosal spread and a known propensity for multiple foci of origin in the regional mucosa (340). Sixty percent to 80% are T₃ or T₄ at diagnosis (345,350,351). A sore throat, dysphagia, and odynophagia are the most common symptoms. Approximately 40% to 60% of the patients will either have, or subsequently develop, positive cervical lymph nodes which may be bilateral (339,345–349,352). The subdigastric, midjugular, and retro- and parapharyngeal lymph nodes are those most often involved.

Tumors of the oropharyngeal wall are especially prone to spread submucosally and through lymphovascular spaces into the nasopharynx above and hypopharynx below. They often invade prevertebral fascia but rarely extend into the anterior spinal ligament.

Treatment and Prognosis

Management of pharyngeal wall carcinomas varies significantly by institution with some advocating primary surgical resection, if possible, and others favoring combined surgery with pre- or postoperative irradiation in advanced lesions (340,347,348,353). Definitive irradiation alone for tumors of all stages has also been advocated (340,354–356). It has been suggested that surgery with or without radiation does not produce improved results over radiation alone but is associated with higher morbidity (340,354).

The literature regarding use of chemotherapy is broad and inconclusive. However, in a study on a group of patients receiving concurrent chemotherapy with irradiation (all of whom had stages T₃ and T₄ tumors), the patients appeared to fare better in overall two-year local control rate than all patients with stages T₃ and T₄ tumors (340). The prognosis of pharyngeal wall carcinoma is extremely poor, regardless of the method of treatment. The average overall five-year survival from several series of cases is 23% (range 3–38%) (339,345–348,352,356). The incidence of second primary malignancies in these patients is significant, varying from 17% to 57% (339,347,348,352). Because of dismal survival rates, only 10% to 20% of the patients live long enough to develop distant metastasis (347,349).

D. Squamous Cell Carcinoma of the Palatine Tonsils and Base of Tongue

The palatine tonsils join the posterior third of the tongue inferiorly through their inferior poles and form the inferior and anterior component of the oropharynx. The base of the tongue harbors the lingual tonsils. Both of the palatine and lingual tonsils are components of the Waldeyer's ring. Microscopically, the tonsils show fissures or crypts, lined with non-keratinized stratified squamous epithelium, that extend into the lymphoid tissue from the surface squamous mucosa of the oropharynx. The lymphoid tissues are composed of germinal centers and diffuse lymphocytes and plasma cells. The latter typically involve the epithelial crypt walls (Fig. 24). The intermingling of lymphoid cells with the epithelium may obscure cytologic features of early carcinomas that may occasionally not be recognized on biopsy examination. The oropharyngeal tonsils are common sites of a distinct clinicopathologic variant of SCC, the *NKCa*, which is etiologically related to high-risk HPV. This variant of SCC will be discussed in some detail below.

Clinical Features

SCC of the tonsil and base of tongue is two-to-five times more common in men and occurs primarily in the 50–70 year age range (52). However, patients with HPV-related carcinomas are generally younger than those who harbor HPV-negative tumors. Significantly, tonsillar carcinomas in patients younger than 40 years are overwhelmingly HPV related (52).

Although SCC of the tonsils and base of tongue has been known to be closely linked to alcohol and

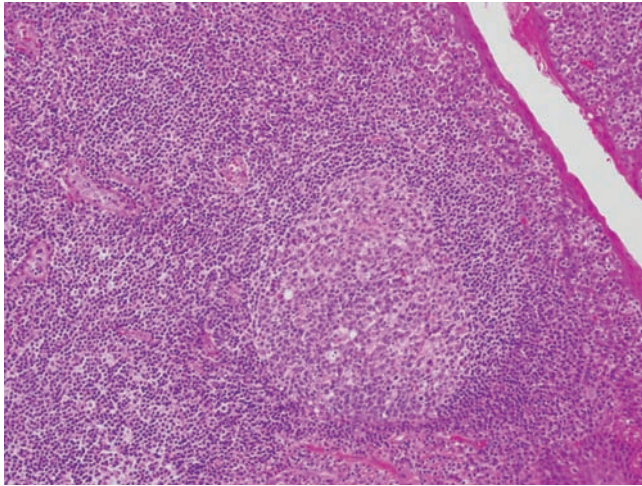


Figure 24 Section in a palatine tonsil showing germinal center and diffuse lymphocytic infiltrate involving the epithelial lining of a crypt wall (100 $\times$).

tobacco use, it has been more recently shown that sexual transmission may play an important etiologic role in patients with HPV-positive carcinomas. The latter patients are three times as likely to report having had oral sex as those with HPV-negative tumors and were more likely to have had multiple sex partners (357). It has also been demonstrated that husbands of women with cervical cancer had a significantly increased risk of developing tonsillar carcinoma (358). At the same time, many patients with HPV-positive carcinoma have little or no exposure to the chemical carcinogens from tobacco and alcohol. HPV is less frequently detected in cancer biopsies of patients who are tobacco smokers or paan chewers (9,10,13,57,171,357,359,360). In a recent, large case-control study of oropharyngeal cancer, it was reported that HPV carcinomas were identified in patients with and without the established risk factors of tobacco and alcohol use (51).

The most common presenting symptom is sore throat. More advanced disease may be associated with dysphagia, referred otalgia, bleeding, trismus, sensation of a foreign body in the throat, and "hot potato" voice in the case of base of tongue carcinomas (361–363). It is not uncommon in cases of HPV-related nonkeratinizing carcinoma that the patient present with cervical lymphadenopathy in the absence of clinically identifiable primary tumor (364,365). Indeed, identification of HPV by in situ hybridization (ISH) and p16 immunoreactivity in SCC metastases to cervical lymph nodes was shown to be a reliable way to establish origin from the tonsils or base of tongue (366,367). HPV-related nonkeratinizing carcinomas typically arise within the tonsillar crypts and may show no mucosal abnormality or any detectable enlargement. On the other hand, conventional KSCC presents, on examination, as an ulcer with rolled, firm margins with infiltrative growth that is palpable. Deep infiltration into the base of tongue is manifested by

inability to protrude the tongue. Tonsillar carcinomas tend to involve the base of tongue, soft palate, and pharyngeal wall. Earlier lesions may present as erythroplakia or as a slight mucosal granularity.

At the time of presentation, 50% to 80% of the patients have clinically positive lymph nodes, 20% to 30% base of tongue carcinomas, and those of the palatine tonsils that involve the tongue base either have or will develop bilateral or contralateral nodal metastasis at some time during the course of the disease (362,368–379).

Treatment and Prognosis

Surgery and radiation either alone, or in combination, are used for treatment of base of tongue and tonsillar carcinomas. Numerous papers have been published on the validity of different treatment modalities. Generally speaking, a combination of surgery and radiation and, in selected cases, surgery and chemoradiation are used for advanced disease (T₃ and T₄), while T₁ and T₂ tumors can be safely managed with either surgery or radiation (380–391).

Key factors in surgical treatment of large base of tongue carcinoma are the proper management of the larynx and OT. Partial or total laryngectomy may be required in some cases (392). The decision to remove the larynx is based on whether it is involved with the tumor (Fig. 25), the amount of tongue to be resected, the status of the hypoglossal nerves, and the general condition of the patient, especially for respiratory function and ability to tolerate aspiration while trying to relearn to swallow (393).

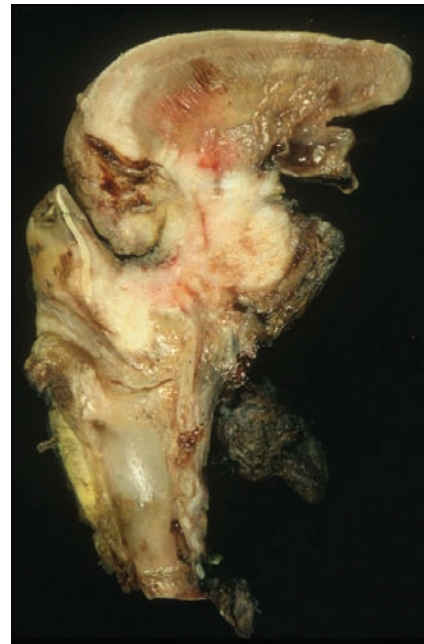


Figure 25 Gross specimen showing SCC of the base of tongue involving the supraglottic larynx, treated by combined glossectomy and laryngectomy. *Abbreviation:* SCC, squamous cell carcinoma.

If less than half of the tongue base is excised, supraglottic laryngectomy can be performed in otherwise healthy individuals without significant operative problems. If, on the other hand, a large portion of the base of the tongue needs to be removed, with sacrifice of both hypoglossal nerves, a total laryngectomy is generally indicated to prevent severe aspiration (393).

Total glossectomy may be required in some patients to achieve an adequate resection margin (394). In a few highly selected patients, total glossectomy without total laryngectomy can be performed (395). For these reasons, some clinicians prefer primary radiation therapy over surgery. Better survival and functional outcome is reported after radiation therapy or chemoradiation in patients with advanced disease (384,386,391). Radiation alone was also shown to produce significantly improved posttreatment function and quality of life compared with other modalities (391).

In a study from Memorial Sloan-Kettering Cancer Center, it was found that most patients obtain long-term regional control, with no severe complications, after definitive radiation therapy, of base-of-tongue carcinoma, followed by neck dissection for those patients who present with lymphadenopathy (386). On the other hand, a study from M.D. Anderson Cancer Center found that patients whose neck disease responded completely to radiation, using accelerated fractionated dose, did not appear to need a planned neck dissection (388).

Postoperative adjuvant radiation therapy for patients with stages III or IV SCC of the tonsils who have undergone complete surgical resection is the treatment of choice for many clinicians (380,382,390). The overall five-year survival rate for tonsillar and base of tongue carcinomas has ranged from 20% to 54% (361,362,369,372,375,380,382,384,391,394–400). The five-year disease-specific survival rates are stage dependent. Survival rates for stages I to IV in tonsillar carcinoma are 93%, 57%, 27%, and 17%, respectively (362). The five-year survival rates for stages I to IV base-of-tongue carcinoma are reported as 100%, 57%, 20%, and 0%, respectively (371). Fifteen percent of the patients develop distant metastasis (401). The most frequent sites of dissemination, in order of frequency, are lung, liver, bones, and brain.

The overwhelming cause of treatment failure and death is local recurrence. Distant metastasis accounts for only a few cases. The five-year actuarial risk of distant metastasis in patients whose disease was controlled locoregionally was 21% in one study (388) and 7.5% in another (389).

Accumulating body of evidence in the United States, as well as the international literature, confirms that HPV-related carcinomas of the tonsils and base of tongue have a statistically significant better prognosis than HPV-negative carcinomas. The favorable outcome is evident in disease-free and overall survival of the patients and is independent of TNM stage, nodal status, age, or gender (402–407). It is suggested that the favorable prognosis is attributable to higher sensitivity toward radiotherapy.

E. Pathology of Squamous Cell Carcinoma Variants

The following variants of KSCC are discussed:

1. NKCa and nonkeratinizing undifferentiated carcinoma
2. BSC
3. ASC
4. Adenoid squamous carcinoma
5. VC
6. Papillary squamous carcinoma
7. Spindle cell (sarcomatoid) carcinoma

IX. NONKERATINIZING SQUAMOUS CELL CARCINOMA

NKCa is a distinct type of carcinoma, which is HPV related. It differs from conventional KSCC, not only microscopically but also molecularly and clinically. The role of HPV infection, as a prerequisite for the development of a great majority of carcinomas of the uterine cervix, is well established (408) and supported by molecular, serologic, and epidemiologic evidence. Similar documentation has also been, more recently, provided for a role for HPV, particularly type 16, in the pathogenesis of a subgroup of SCCs of the head and neck (361,409–411). Genomic DNA of high-risk HPV is detected in approximately 26% of all SCCs of the head and neck worldwide (412). Rigorous and consistent molecular evidence have shown viral integration and the expression of viral oncogenes (E6 and E7) in nonkeratinizing oropharyngeal carcinomas of the tonsils and base of tongue (52,54,410,411,413). The prevalence of HPV DNA, particularly type 16, in oropharyngeal carcinomas has varied in different studies from 18% to 90% (52,54–57,411). A variety of techniques are used to identify HPV in the tumors, including ISH, polymerase chain reaction (PCR), and immunohistochemistry. The virus is less frequently identified in laryngeal and sinonasal carcinomas and rarely in oral SCC (52–54).

In a review of 235 oropharyngeal carcinomas in all age groups by El-Mofty and Patil (54), 36% of tonsillar and 32% of base of tongue carcinomas were HPV-related NKCa. Alternatively, 91% of tonsillar carcinomas in young patients (younger than 40 years) were HPV type 16 positive (52). The average age for patients with NKCa of the tonsil and base of tongue was found to be 53.6 and 56.6 years, respectively. On the other hand, patients with conventional KSCC are slightly older with an average age of 56.6 and 58.0 years, for tonsillar and base of tongue, respectively. The male-to-female ratio for patients with HPV-related NKCa of the tonsils and base of tongue is 4:1 (54). Numerous epidemiologic and case-control studies provide support for the association of high-risk sexual behavior with HPV-related oropharyngeal cancer (51,357,414–420).

Patients with HPV-positive tumors were three times as likely to report having had oral sex as those with HPV-negative tumors and were also more likely to have had multiple sex partners (51,357). An analysis

of the Swedish Cancer Registry data (1958–1996) showed that husbands of women with cervical cancer had significantly increased risk of developing tonsillar cancer (358). Exposure to HPV increases the association with oropharyngeal cancer, regardless of tobacco and alcohol use. HPV is less frequently detected in cancer biopsies from patients who are tobacco smokers or paan chewers (9,10,357). These observations suggest two distinct pathways for the development of oropharyngeal cancers of the tonsils and base of tongue. In the case of the KSCC, the process is driven predominantly by the carcinogenic effects of tobacco or alcohol (or both). The other pathway, as in the case of the NKCa, is by HPV-induced genomic instability.

A. Microscopic Features

HPV-related SCCs are characterized by nonkeratinizing basaloid morphology. The tumor cells are generally monomorphic, oval, or spindle shaped, with hyperchromatic basophilic nuclei, inconspicuous cytoplasm, and indistinct cell borders. They form cords, sheets, and nests with sharply defined borders (Fig. 26). Palisading of the peripheral cells may be present (Fig. 27). Excessive mitoses and apoptosis as well as comedo-type necrosis are commonly observed (Fig. 28). Keratinization and keratin pearl formations are generally absent, although some trend toward keratinocytic maturation may occasionally be present focally in some tumors (Fig. 29). In these hybrid lesions, the basaloid epithelial cells at the center or the periphery of the neoplastic cell sheets may show keratinocytic rather than basal cell morphology (Figs. 29, 30). The metaplastic change is manifested by a more prominent cytoplasm, distinct cell membrane, and intercellular bridges.

HPV-related nonkeratinizing carcinomas typically start deep in the tonsillar crypts of both the

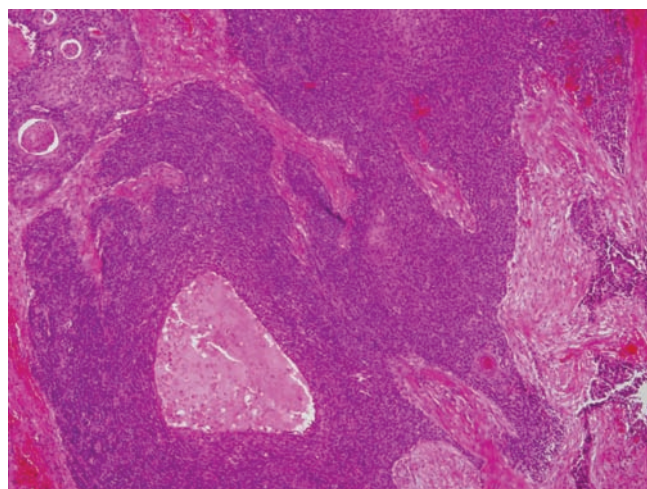


Figure 26 NKCa of the oropharynx. Sheets of neoplastic cells with sharp outline and comedo-type necrosis (100×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

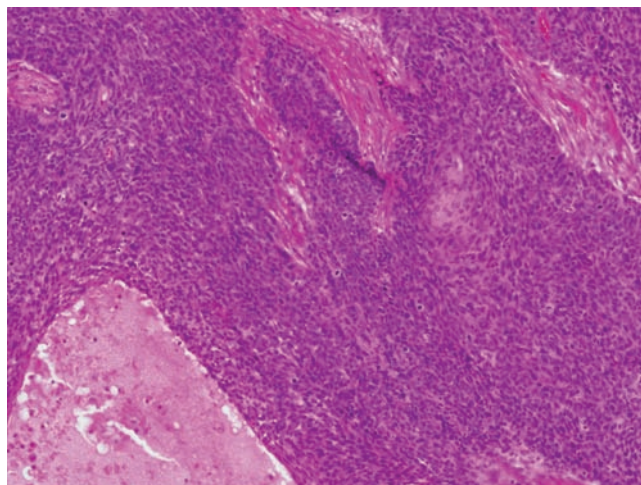


Figure 27 NKCa. Oval and spindle shaped cells with hyperchromatic nuclei, inconspicuous cytoplasm and indistinct cell borders (200×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

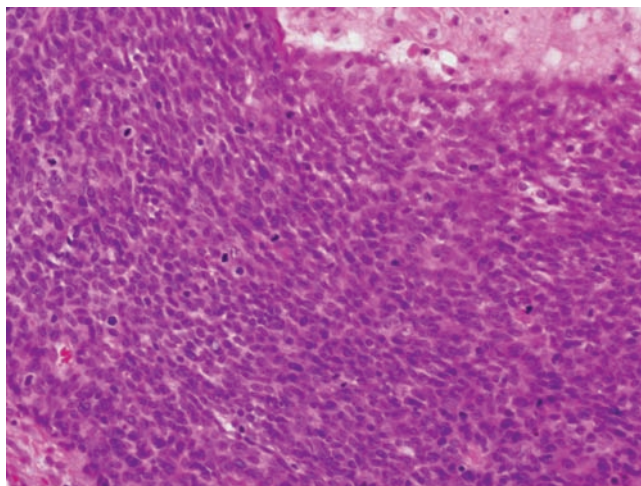


Figure 28 NKCa showing excessive mitoses and apoptosis (400×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

palatine and lingual tonsils. Because of such location, the early lesions may be inaccessible to cytologic smears and superficial biopsies (Fig. 31). It is not uncommon that small primary tumors, which are undetectable on routine clinical and radiographic examination, are associated with significant cervical lymph node metastasis. These occult primary carcinomas are typically missed on multiple blind endoscopic biopsies of suspect sites. However, it has been found that microscopic identification of HPV-related NKCa or the detection of HPV by ISH and/or p16 immunostaining in metastatic cervical lymph nodes are

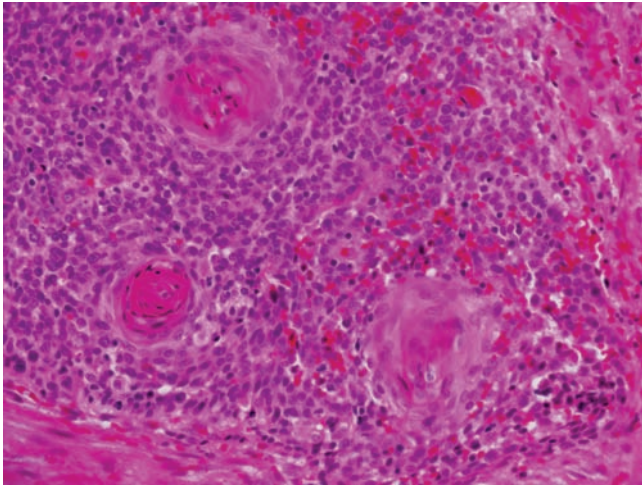


Figure 29 NKCa with focal areas of keratinocytic maturation (400×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

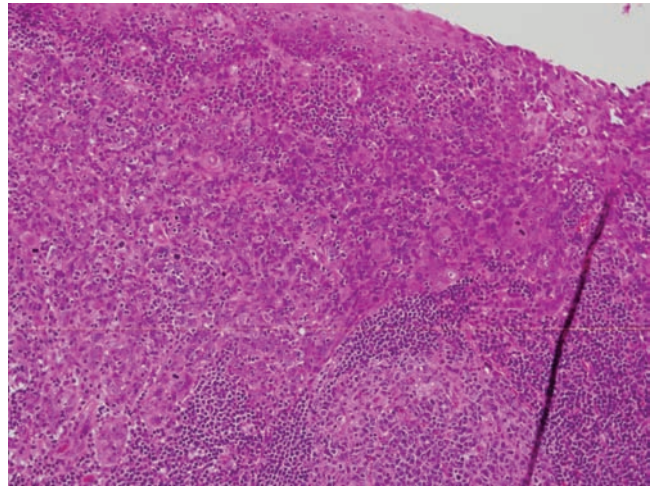


Figure 31 NKCa arising deep in the wall of a tonsillar crypt (200×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

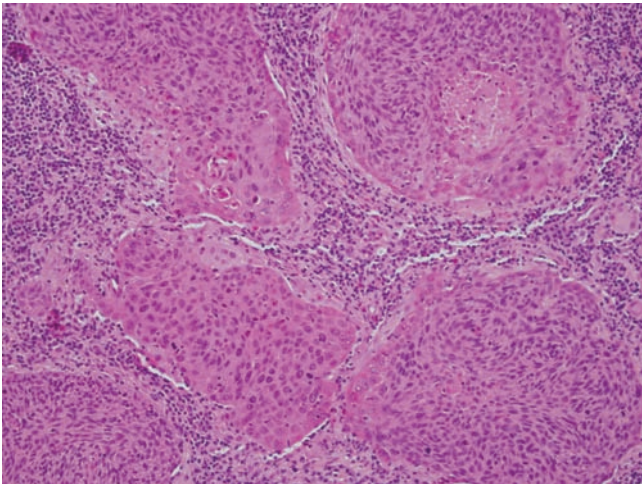


Figure 30 NKCa. Notice maturation of the peripheral cells (200×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

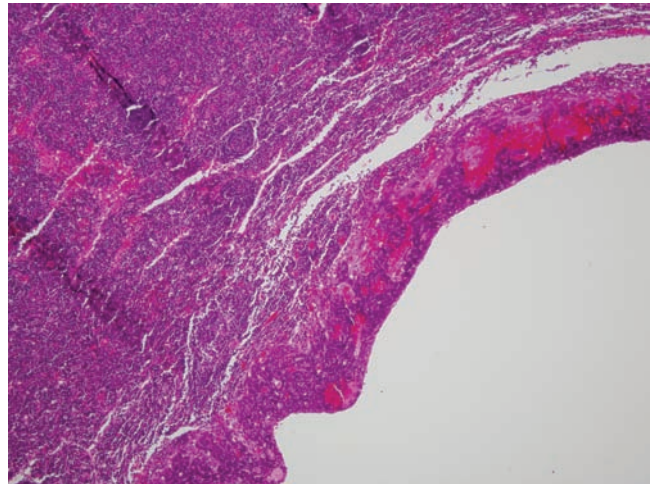


Figure 32 Cystic changes in NKCa metastatic to a cervical lymph node (100×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

reliable techniques for establishment of the origin of an occult tonsillar carcinoma. These primary carcinomas are best identified in excisional biopsies of the palatine or lingual tonsils (366,367,421). Identification of the site of a clinically occult primary carcinoma is crucial for the proper management of the patients. In the absence of a known primary tumor, patients with cervical metastasis are likely to be overtreated with wide-field irradiation that includes the entire pharyngeal axis and larynx. Such treatment protocols are associated with severe morbidity (422–424). Nonkeratinizing carcinoma metastasis to lymph nodes commonly exhibits extensive central necrosis leading to

characteristic cystic change. The lining epithelium of the cystic structures may be so scant and bland appearing that a misdiagnosis of benign cyst may be rendered (Fig. 32). Such an error is more likely made in patients whose primary tumors are occult.

B. Immunohistochemistry

The immunohistochemical profile of nonkeratinizing carcinoma differs from that of the conventional KSCC in several aspects. A major distinction is that nonkeratinizing carcinoma shows a diffuse and strong reactivity to p16 antibodies (Fig. 33), while KSCC is

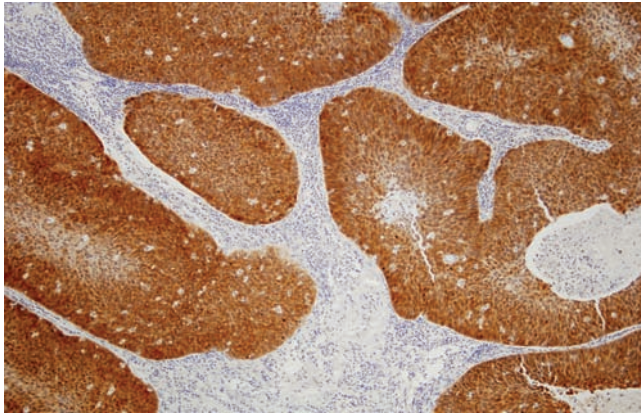


Figure 33 NKCa showing strong and diffuse nuclear and cytoplasmic reactivity for p16 immunostain (200×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

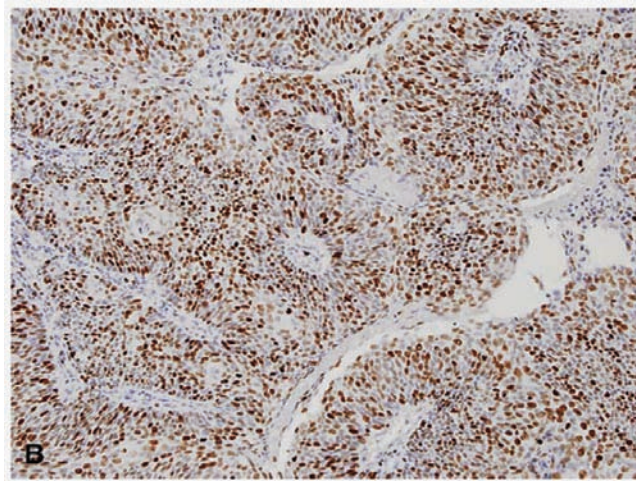


Figure 34 High staining scores for Ki67 in an NKCa (200×). *Abbreviation:* NKCa, nonkeratinizing squamous cell carcinoma.

either negative or weakly and focally positive (52,54). More over, an inverse staining pattern is observed with p53 reactivity. KSCC is much more likely to react positively and strongly to this antibody than nonkeratinizing carcinoma. Another distinction is observed in immunostaining for Ki67. Nonkeratinizing carcinoma shows much higher staining scores, with that marker, than KSCC (Fig. 34) (52,54).

Overexpression of p16 has been extensively documented in HPV-related carcinomas of the uterine cervix and anorectal tract (425–428) and more recently, as stated above, in nonkeratinizing carcinoma of the oropharynx. p16 is considered as a surrogate biomarker for HPV-related carcinomas.

p16 gene product INK4A protein is a cell cycle protein associated with the retinoblastoma pathway. It

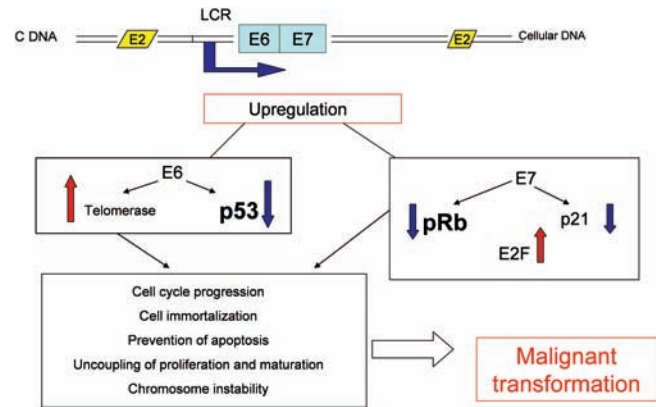


Figure 35 Schematic representation of the proposed interaction of HPV E6 and E7 oncoprotein with cell cycle regulators p53 and Rb.

prevents the dissociation of E2F transcription factor from pRb and the subsequent progression of S-phase of the cell cycle (87,429,430). The paradoxical overexpression of an inhibitory protein in actively replicating neoplastic cells is thought to result from feedback control secondary to pRb deregulation by HPV E7 oncoprotein (427,431) (Fig. 35).

The increased mitotic activity of nonkeratinizing carcinoma as compared with KSCC is well illustrated microscopically (Fig. 28) and is documented by higher Ki-67 labeling scores (52,54) (Fig. 34). Ki-67 is a nuclear protein that is overexpressed in actively proliferating cells. A high Ki-67 score has also been used as a surrogate biomarker for HPV-related carcinoma of the uterine cervix (427,432,433).

The inverse correlation between NKCa and p53 has also been documented in HPV-related carcinomas in several studies, immunohistochemically as well as by molecular-sequencing techniques (52–54,431,434). It is well known that p53 mutations play a significant role in development of the majority of conventional KSCC in patients with known environmental risk factors, such as tobacco and alcohol abuse (434–436). However, in the case of HPV-related carcinomas, p53 inactivation is achieved by a different process. HPV-E6 oncoprotein interferes with p53 function by targeting it for ubiquitination and degradation (87,437).

X. NONKERATINIZING UNDIFFERENTIATED CARCINOMA

Nonkeratinizing undifferentiated carcinoma is a variant of NKCa. It is also known as lymphoepithelioma and nasopharyngeal-type lymphoepithelial carcinoma. Undifferentiated carcinoma is rare, accounting for 0.8% to 2% of all oral/pharyngeal carcinomas. More than 90% of this type of carcinoma occurs in the tonsils and base of tongue (438–441). The patients may present

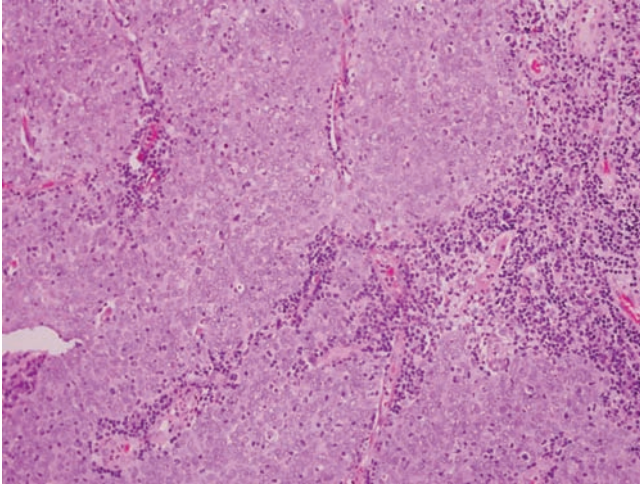


Figure 36 Undifferentiated carcinoma of the palatine tonsil. Notice morphologic similarities to nasopharyngeal undifferentiated carcinoma (lymphoepithelial carcinoma) (200 $\times$).

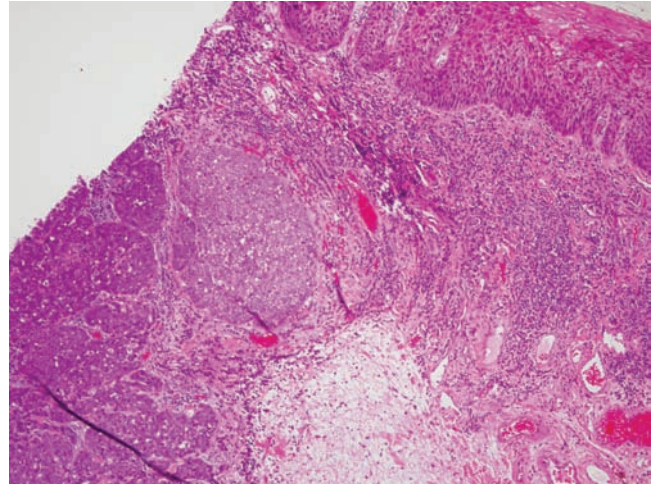


Figure 37 BSC. Dysplastic surface epithelium at upper right corner (100 $\times$). *Abbreviation:* BSC, basaloid squamous carcinoma.

with an oropharyngeal mass or a neck mass. Cervical lymph node involvement occurs in approximately 70% of the cases at presentation (439,441,442).

Microscopically, undifferentiated carcinoma of the oropharynx shows morphologic features that are indistinguishable from that of the nasopharyngeal undifferentiated carcinoma (WHO type III). The tumor is composed of syncytial sheets and clusters of carcinoma cells with vesicular nuclei and prominent nucleoli and ill-defined cell borders. A rich lymphocytic infiltrate surrounds the tumor cells (Fig. 36). ISH for Epstein-Barr virus (EBV)-encoded RNA is usually negative in Caucasians but may be positive in Chinese patients (443,444). A relationship of undifferentiated carcinoma of the oropharynx to HPV is suspected but presently unconfirmed. The tumor cells are positive for pan-cytokeratin and epithelial membrane antigen (EMA) immunostains and are negative for leukocyte common antigen (CD45).

Undifferentiated carcinoma of the oropharynx is radiosensitive. Local, regional, and distant failure occurs in 3%, 5% and 19%, respectively. Distant metastasis is associated with poor prognosis.

XI. BASALOID SQUAMOUS CARCINOMA

The histologic features of BSC were first defined in 1986 by Wain et al. (445). The tumor is an aggressive variant of conventional SCC. It is described as having biphasic morphologic features: a basaloid pattern, which is intimately associated with KSCC, dysplastic surface epithelium (Fig. 37), carcinoma in situ, or with focal areas of squamous differentiation. The squamous differentiation is identified by the presence of two or more of the following histologic features: (i) individual cell keratinization, (ii) intercellular bridges, (iii) keratin pearl formation, and (iv) cells arranged in

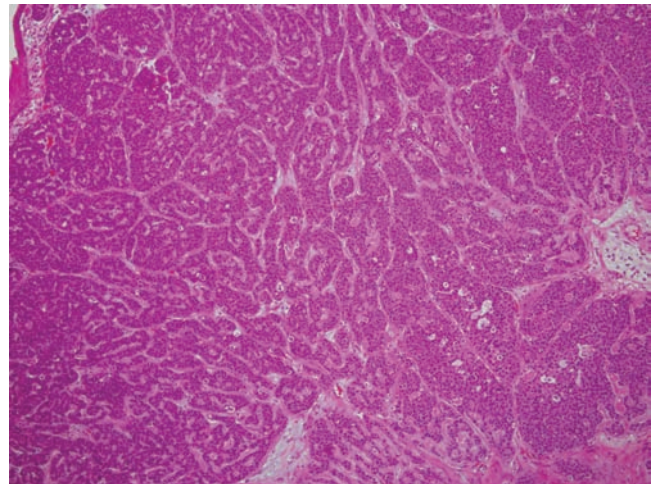


Figure 38 BSC. Closely opposed lobules and sheets forming a jigsaw puzzle pattern (100 $\times$). *Abbreviation:* BSC, basaloid squamous carcinoma.

a paving pattern. The basaloid component is described as having the following principle histologic features: (i) solid groups of cells in a lobular configuration that are closely opposed, producing a jigsaw puzzle appearance (Fig. 38), (ii) small crowded cells with scant cytoplasm, (iii) dark hyperchromatic nuclei without nucleoli, (iv) small gland-like cystic spaces (Fig. 39), (v) small and large foci of coagulative necrosis within the central areas of the tumor lobules, (vi) stromal hyalinization and intercellular hyaline deposits (Figs. 40, 41).

BSC occurs predominantly in the upper aerodigestive tract. Seven of the 10 cases originally described

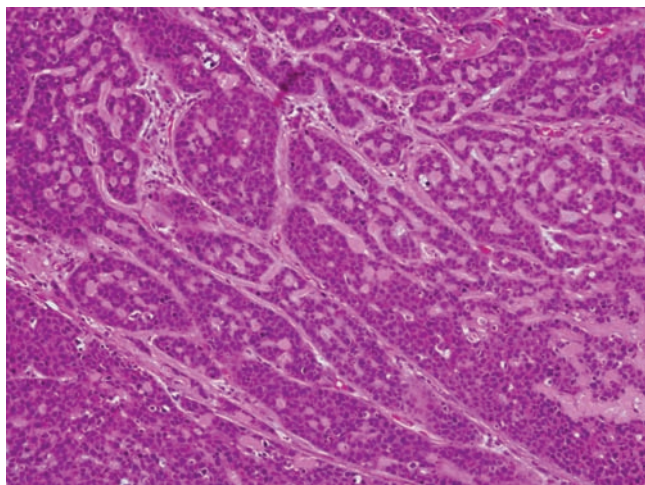


Figure 39 BSC with pseudoglandular appearance reminiscent of ACC (200×). *Abbreviations:* BSC, basaloid squamous carcinoma; ACC, adenoid cystic carcinoma.

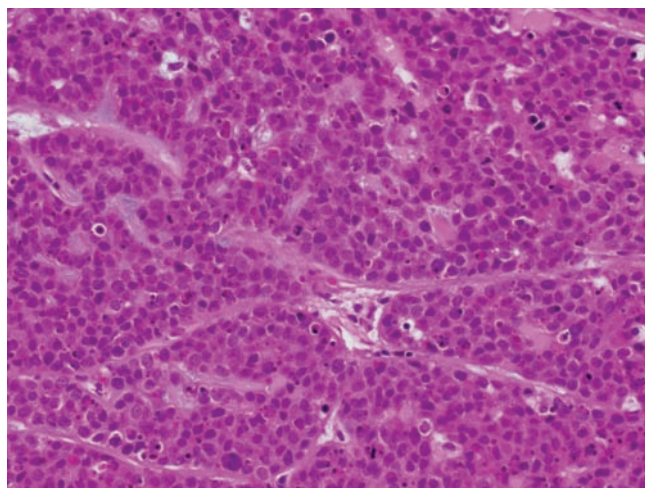


Figure 40 Peripheral palisading of the neoplastic cells, stromal hyalinization, excessive mitosis, and apoptosis in BSC (400×). *Abbreviation:* BSC, basaloid squamous carcinoma.

arose from the pyriform sinus of the hypopharynx, and/or the epiglottis, and three from the base of tongue. In a review of 40 cases of BSC (446), 13 occurred in the pyriform sinus, 12 base of tongue, 8 larynx, 5 tonsils, and 2 nasal cavities. Luna et al. (447) in their report of nine cases of BSC found seven cases in the pyriform and pharyngeal wall and two in the base of tongue.

In another study of 12 cases of BSC, 10 arose in the pyriform sinus, epiglottis, and base of tongue (448). BSC is less frequently reported in the sinonasal tract (449,450) and rarely in the oral cavity proper, including the palate, FOM, buccal mucosa, and gingiva

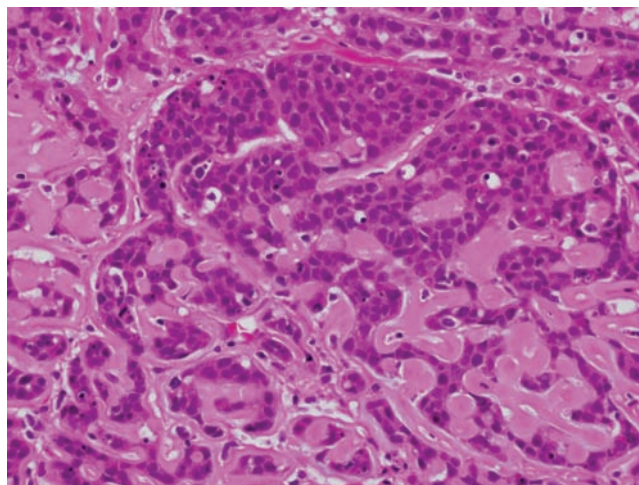


Figure 41 BSC showing deposits of intercellular hyaline material (400×). *Abbreviation:* BSC, basaloid squamous carcinoma.

(451–458). Most oral and sinonasal BSC are reported as single cases, and in some of them, the microscopic features did not conform strictly to the histologic criteria necessary for diagnosis of BSC, as originally defined by Wain et al. (445). It is clear from review of the literature that well-documented cases of BSC have a predilection for the pyriform sinus, supraglottic larynx, and base of tongue (445–450,459).

BSC of the upper aerodigestive tract affects, overwhelmingly, male patients with male-to-female ratio ranging from 7:1 to 11:1 (445,447,448). The patients tend to be elderly, with a mean age varying from 58.5 to 64 (range 49–88) (445–447,459). A history of heavy smoking and alcohol abuse is reported in the majority of cases (446,447,458,460). A possible role for radiation in the etiology of BSC was suggested in a case in which the tumor developed in the nose of a Chinese patient 12 years after radiotherapy for nasopharyngeal carcinoma (449).

A. Treatment and Prognosis

BSC is a highly malignant variant of SCC with a propensity to aggressive local behavior and early regional and distant metastasis with subsequent poor survival (445–447,459,461,462).

Most patients are managed with radical surgery supplemented with radiation and/or chemotherapy. The great majority of the patients present with stages III or IV disease (446,447,463). Cervical lymph node metastasis is reported in 60% to 78% of the patients at initial diagnosis (445–447,450,459). Distant metastasis is observed in 38% to 48% of cases. Metastatic lesions are found more commonly in the lungs but may affect the liver, bones, and central nervous system (445,446,459). At least half of the patients die of the disease one-to-four years after presentation (445,446,450,459,462–464). Evidence for prognostic significance of

tumor cell ploidy as measured by flow cytometry is contradictory. One study found that patients with aneuploid BSC had a better mean survival time (39.5 months) than those with diploid carcinoma (16.3 months) (447). Alternatively, tumor ploidy provided no additional prognostic information in another investigation (459). Comparing the clinical outcome of BSC and poorly differentiated SCC, Winzenburg et al. (465) found that patients with BSC had had more advanced disease at presentation, less than half the survival rate, and more frequent distant metastasis. Distant metastasis, in this study, occurred in 52% of patients as compared with 13% of patients in the poorly differentiated SCC group. An increase in the incidence of second primary carcinomas in the upper aerodigestive tract has been indicated as well (460).

B. Immunohistochemistry

Most immunohistochemical studies show positive reactivity of the tumor cells to keratin markers, including high- and low-molecular weight cytokeratins (pancytokeratins) AE1/AE3, CAM 5.2, and to high molecular weight cytokeratin 34 β E12 (409,446,448, 450,466). The staining may be diffuse in the squamous and basaloid components of the carcinoma or may be more intense in the squamous or the basaloid areas (446,448,450). However, the staining pattern is never punctate paranuclear (409,446). EMA is reported to be positive in most cases, but may vary in intensity and focality (446). Strong and diffuse p63 immunoreactivity was reported in 100% of the tumor cells (475). Although neuron specific enolase (NSE) is reported to be reactive in up to 75% of cases of BSC in some studies (446,448,450), others found it to be negative in all cases (466). Focal reactivity for S-100 protein is reported by some investigators, in some of the cases (456,467). Others found no reactivity in the tumor cells (467,468) or was limited only to the Langerhan's cells in the tumors (448). Other markers such as chromogranin, synaptophysin, GFAP, LCA, HMB-45, and desmin are negative (446,450,466,469). Vimentin and actins may either be negative or infrequently positive (409,448,470). Cell cycle regulator biomarkers in BSC were evaluated in several studies. High labeling scores for p53 and Ki67 were reported in the majority of cases studied (463,471–473). Low expression of p27, a cyclin dependent kinase inhibitor, correlated independently with poor prognosis. Brisk labeling for Ki67, p53, and low expression of E-cadherin also corresponded to poor prognosis (463). More aggressive behavior, as compared with conventional SCC, was found to be associated with overexpression of matrix metalloproteins MMP-1 MMP-2, and MMP-9, in addition to higher staining scores for p53 (472).

Using PCR, Cabanillas et al. (471) found no evidence of HPV in nine cases of BSC. Similarly, ISH for HPV failed to demonstrate the virus in another nine cases of BSC (466). Other ISH studies also did not show EBV RNA to be present in any of the 23 cases of BSC (409).

C. Differential Diagnosis

Before its definition as a variant of SCC, BSC was often confused with the solid variant of adenoid cystic carcinoma (ACC). Features such as the basaloid cytologic morphology, cystic, glandular-like spaces and intercellular hyaline deposits are analogous to those seen in ACC. However, a major histopathologic feature of BSC is the presence of definable elements of squamous cell differentiation, which may be in situ or invasive carcinoma, and as focal areas with squamous features. ACC lacks that characteristic. In addition, BSC tends to exhibit higher-grade nuclear morphology, with more pleomorphism, mitoses and apoptosis, than seen in cases of ACC (459). Although these histopathologic differences may be sufficient for correct diagnosis, occasionally, especially in small biopsies, the distinction may be difficult. In such cases, immunohistochemical evaluation may be required.

The myoepithelial elements in ACC typically react positively to vimentin, muscle actins, and S-100 protein, in addition to cytokeratin. BSC, on the other hand, lacks myoepithelial components and is typically negative for those markers (409,448,471). Vimentin immunoreactivity may be present in some BSC. In these cases, the pattern of staining is peculiar, forming a delicate perinuclear rim with a small dot (474). Coletta et al. (454) reported positive staining with laminin and type IV collagen, in the microcystic spaces of BSC, which was not found in ACC. In a more recent study, p63 immunostaining was used to distinguish ACC from BSC (475). BSC consistently displayed diffuse p63 positivity with staining of nearly 100% of tumor cells. On the other hand, ACC showed either selective staining of single peripheral layer or focal compartmentalization pattern of staining. Distinction of BSC from ACC has important clinical and prognostic implications. Treatment of BSC is usually surgery with neck node dissection in addition to radiotherapy and, in advanced cases, chemotherapy. ACC is usually treated with only excision of the primary tumor.

BSC may present many similarities to small cell neuroendocrine carcinomas, particularly in small biopsies. Small cell neuroendocrine carcinoma uniformly react to pancytokeratin antibodies AE1/AE3 and CAM 5.2 frequently (60–80%) in a paranuclear pattern, while BSC does not show such staining pattern (409). The high molecular weight cytokeratin 34 β E12 is positive in BSC but not in neuroendocrine carcinoma (409,471). Although some BSC show positive reactivity to NSE, none are reactive to other neuroendocrine markers such as synaptophysin and chromogranin. Alternatively, as expected, neuroendocrine carcinomas show positive reactivity to all of the neuroendocrine markers (409,469,471,474,476).

HPV-related nonkeratinizing carcinoma shares with BSC a basal cell morphology and the base of tongue as a common anatomic location. For these reasons, cases of nonkeratinizing carcinomas are occasionally misdiagnosed as BSC. Distinction between these two variants of SCCs is of utmost importance for proper management and accurate prognosis. When

compared with NKCa, BSC is rare, more biologically aggressive, less responsive to radiation therapy, and has a much worse prognosis.

Microscopically, NKCa shows basaloid morphology, but unlike BSC, NKCa never shows the microcystic glandular patterns seen in BSC, and it is not associated with conventional SCC or areas of frank keratinization. However, NKCa, as mentioned above, may show areas of maturation, producing a pattern that may be compared with BSC. NKCa is consistently associated with high-risk HPV infection. HPV DNA is invariably demonstrated in these tumors by PCR, ISH, and other molecular techniques. So far, HPV has not been documented in BSC (461,466,471), using either PCR (471) or ISH (461,471) techniques.

XII. ADENOSQUAMOUS CARCINOMA

The term adenosquamous carcinoma (ASC) was proposed by Gerughty et al. (477) to describe a biphasic neoplasm composed of two components, adenocarcinoma and SCC (Figs. 42–44). The SCC can be in situ or invasive, ranging from well-to-poorly differentiated. Squamous differentiation is defined by paved growth with intercellular bridges, keratin pearl formation, dyskeratosis, and/or individual cell keratinization. The adenocarcinoma component can be tubular, alveolar, or glandular. Mucous cells may be present but are not a prerequisite for diagnosis. The two carcinomas may be separate or intermixed, with areas of comingling and/or transition of the squamous carcinoma to adenocarcinoma (477–482). The relative abundance of the two carcinomas varies in different tumors, the squamous carcinoma may dominate in some while, less frequently, adenocarcinoma dominates. Equal distribution of the two components may be observed in some cases (479).

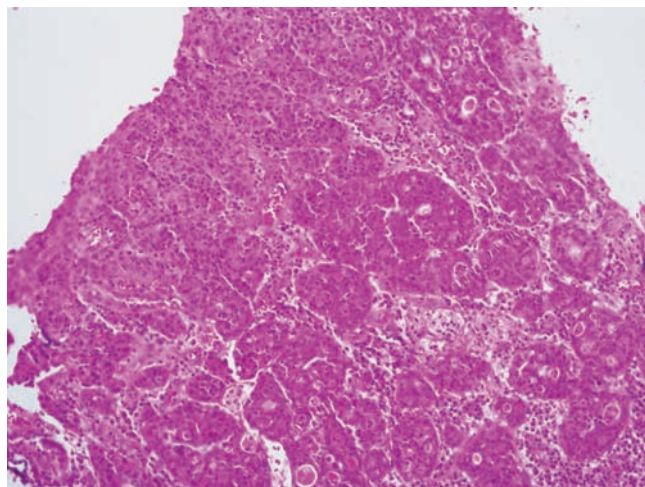


Figure 42 Adenosquamous carcinoma of the soft palate. Surface poorly differentiated SCC with deeper adenocarcinoma (20 $\times$). *Abbreviation:* SCC, squamous cell carcinoma.

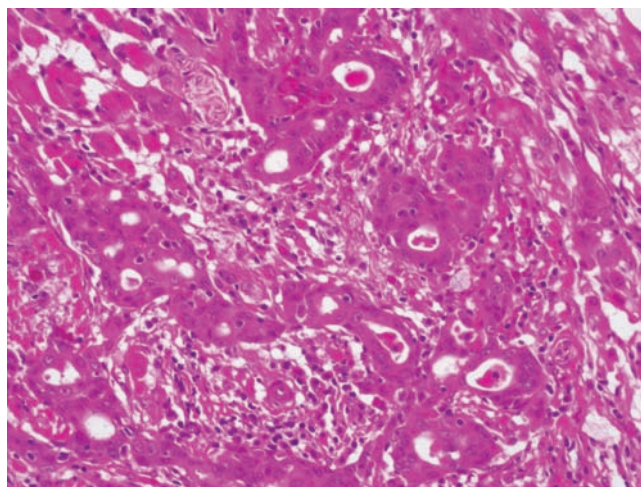


Figure 43 ASC, higher magnification of the adenocarcinoma component (200 $\times$).

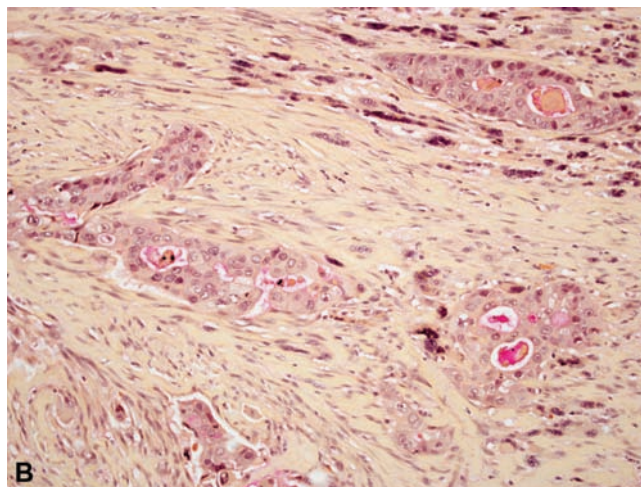
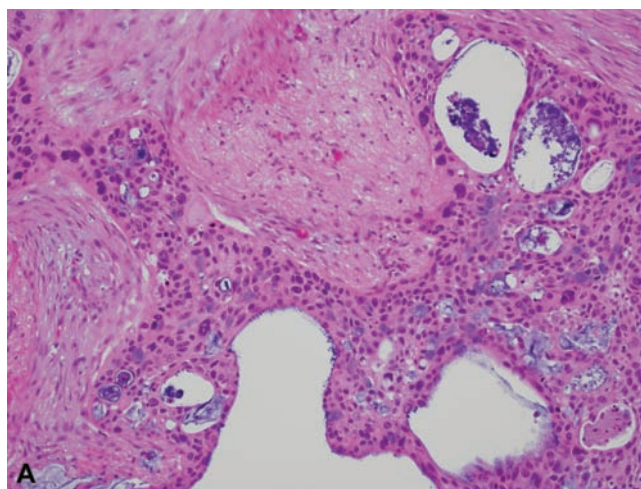


Figure 44 (A) ASC, notice areas of comingling of squamous carcinoma and adenocarcinoma. (B) ASC, mucicarmine stain (200 $\times$). *Abbreviation:* ASC, adenosquamous carcinoma.

ASC develops from surface as well as glandular epithelium. In addition to the upper aerodigestive tract, ASC has been reported in the skin, lung, stomach, ileum, colon, gallbladder, endometrium, liver, pancreas, kidney, thyroid, and prostate among other sites (467,470,478,483–489). In the upper aerodigestive tract, the larynx is the most frequently reported site followed by, in order of frequency, FOM, tongue, tonsil, nasal cavity, and alveolar mucosa, less commonly the buccal mucosa, lip, palate, and nasopharynx (479). In a review of oral cases examined at the Armed Forces Institute of Pathology (AFIP), the tongue, FOM, tonsil, and soft palate accounted for 85% of the cases. The buccal mucosa, RMT, and lip are the other sites of occurrence (490). In a review of 58 cases of ASC of the upper aerodigestive tract reported in the English literature, Keelawat et al. (479) found that the patients' age range was 34–81 years, with a median age of 61.5 years. The male patients outnumbered females by a ratio of 4.3:1. A history of smoking, smokeless tobacco use, and alcohol was common in the majority of cases (479). A history of radiation has also been suggested as a risk factor in a case that involved the mandibular alveolar mucosa (481). Symptoms vary according to site and range from 1.5 to 12 months in duration. Patients with FOM and tongue tumors typically complain of mouth ulcers, pain, indurations, ill-fitting dentures, and a painless mass. Patients with tonsillar tumors may complain of odynophagia, otalgia, and weight loss (479,486).

In spite of relatively few number of cases of oral and oropharyngeal ASC reported with adequate follow-up, there is general agreement that this variant of SCC is extremely aggressive and treatment resistant (477,479–481,486,491,492). Most patients present with advanced-stage disease, early nodal metastasis, later distant metastasis, and generally fatal outcome. Sites of distant metastasis include lungs, liver, bone, brain, and kidney. Radical surgery with neck dissection is the treatment of choice. Adjuvant radiation and/or chemotherapy, with few exceptions, do not appear to offer any therapeutic advantages (477,479,491).

A. Immunohistochemistry

Few studies have investigated the immunohistochemical profile of oral/pharyngeal ASC (478,480,491). The tumors show differences in staining patterns between the squamous carcinoma and adenocarcinoma elements in the tumors. The former react positively to high molecular weight cytokeratin and negative for low molecular weight cytokeratin and carcinoembryonic antigen, whereas the reverse is true of the glandular components.

B. Differential Diagnosis

Two main entities are considered in the differential diagnosis for ASC: mucoepidermoid carcinoma and adenoid squamous carcinoma. The later will be discussed in more detail below, in the section on adenoid SCC.

Mucoepidermoid carcinoma, unlike ASC, only arises from glandular and not surface epithelium. Both mucoepidermoid carcinoma and ASC manifest epidermoid and glandular features. However, separate and definitive areas of squamous carcinoma and adenocarcinoma are not seen in mucoepidermoid carcinoma. Keratin pearl formation and individual cell keratinization are extremely rare in mucoepidermoid carcinoma, as compared with ASC, and surface carcinomatous changes are never seen. Although mucicarmine-positive cells may be found in ASC, they are not requisite for diagnosis as in the case of mucoepidermoid carcinoma. Moreover, the distinct aggregates and cyst-lining rows of mucous cells, typical of mucoepidermoid carcinoma, are not present in ASC (490).

XIII. ADENOID SQUAMOUS CARCINOMA

This variant of SCC is also known as pseudoglandular SCC and acantholytic SCC. It occurs most commonly on the sun-exposed skin of the head and neck region. It has been shown to develop in areas of actinic keratosis (493,494). Several cases have been reported in the vermilion border of the lip, most commonly the lower lip (495–499). Of 22 cases of adenoid squamous carcinoma of the lip published in the English literature, only three were in the upper lip and the rest developed in the lower lip (495–499). The lesions affected predominantly males, with a 4.5:1 male-to-female ratio. The mean age of the patients was 55.3 years (range 41–75 years).

Clinically, the lesions have been variously described as keratotic or hyperkeratotic (499), ulcerated (500), exophytic (498), and “warty and irritated” (501). Pain was reported at presentation in some cases. The lesion size varies from 0.2 to 2.0 cm with an average of 1.0 cm. The prominent position of the lesions favors early detection and treatment (495).

Microscopically, the superficial portion of the tumor resembles a typical SCC. However, the deeper extensions demonstrate gland-like structures lined by a single or double layer of cuboidal epithelial cells that exhibit nuclear pleomorphism, hyperchromaticity, and mitotic activity. Scattered acantholytic, dyskeratotic cells are evident in these foci (Fig. 45). The fibrous connective tissue stroma may reveal solar elastosis in addition to an inflammatory cell infiltrate. Solar keratosis with acantholysis may be evident in the adjacent stratified squamous epithelium.

Mucicarmine stains are negative for mucin (495,501). Cases that were evaluated immunohistochemically showed strong positive reactivity to high molecular weight cytokeratins but were not reactive to S-100 protein, factor VIII-related antigen and vimentin (495,501).

The preferred treatment of the lip lesions is local excision. Lymph node metastasis is rare, (495) and so is death related to disease (501). The excellent prognosis may be due to early detection.

Although quite uncommon, a few cases of intraoral adenoid squamous carcinomas have been

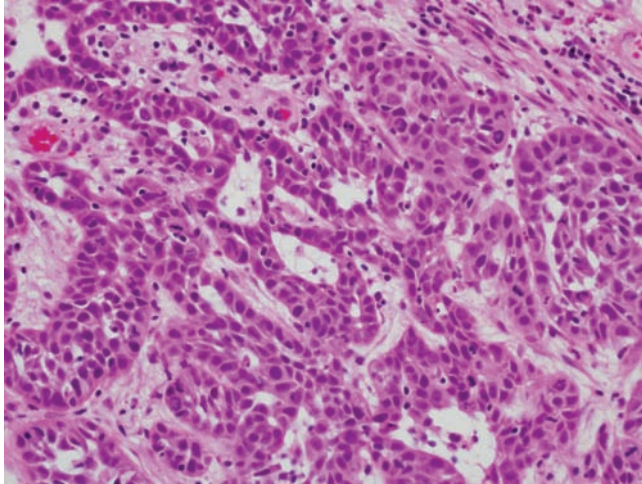


Figure 45 Adenoid squamous carcinoma of the lip showing acantholysis (200 $\times$).

reported. These involved the tongue, maxillary gingiva, and FOM (501–503). These tumors tended to be more aggressive than those occurring in the lip. As previously mentioned, adenoid squamous carcinoma must be differentiated from ASC. Adenoid squamous carcinomas exhibit pseudoglandular spaces that are caused by acantholysis of the tumor cells. No sialomucin is produced and dyskeratotic and acantholytic cells can be found within many of the pseudoluminal spaces. These features contrast with positive mucicarmine staining and the true lumina of the adenocarcinomatous portion of ASC.

XIV. VERRUCOUS CARCINOMA

VC was first defined as a distinct clinicopathologic entity by Lauren Ackerman in 1948 (504). The tumor is described as a locally aggressive, nonmetastasizing variant of well-differentiated SCC. It is characterized by an exophytic, warty, slowly growing neoplasm with pushing margins. VC is still referred to, by some pathologists, as Ackerman's tumor. The oral cavity is the most frequent site of occurrence for VC, accounting for about 75% of all cases (505–507). The larynx is the second most common site constituting 10% to 15% of the cases (506,508). VC has been diagnosed in numerous other anatomic locations within the head and neck, besides the oral cavity and larynx. These include the nasal cavity, maxillary sinus, pyriform sinus, esophagus, middle ear, and skin (482,506,509–515).

In the oral cavity, VC represents 2% to 8% of all SCCs (505,516–518). It is known to be associated with tobacco habits such as snuff, chewing tobacco, and betel nut use (506,516). However, not all cases of VC of the oral cavity are related to tobacco use. HPV types 6, 11, 16, and 18 have been identified in some but not all VCs (506,519–523).

A. Clinical Features

Although VC is primarily a disease of men, between 50 and 80 years of age, it has been described in individuals as young as 34 years (504,506,516,517). There are also some variations in gender according to geographic location. In the southern United States, where the use of snuff is prevalent among women, there is a relative increase of VC in female patients (516). A higher prevalence of VC in women is also observed in patients with proliferative verrucous leukoplakia (PVL) (524,525). PVL is a clinicopathologic entity that was originally described by Hansen et al. (524). It is a continuum of hyperkeratotic disease with high prevalence among elderly women. The condition is detailed in another section of this text.

The majority of oral VC occurs either on the buccal mucosa or the gingiva. Other sites affected, in descending order of frequency, are the labial mucosa, palate, RMT, or anterior tonsillar pillars (505,526). In most patients, the lesion presents as a slow growing, exophytic, warty mass (Figs. 46, 47) that may be tender or painful. Bleeding is uncommon.



Figure 46 VC of the buccal mucosa involving the alveolar ridge and tongue. *Abbreviation:* VC, verrucous carcinoma.

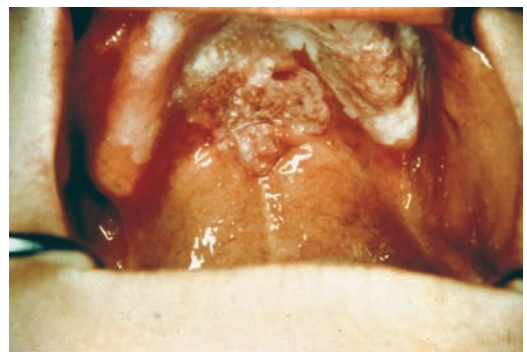


Figure 47 VC of the palate involving the edentulous maxillary alveolar ridge. *Abbreviation:* VC, verrucous carcinoma.

B. Pathology

Grossly the tumor is exophytic, broadly based, gray-white, soft or firm. The lesions size varies from 1 to 10 cm. Microscopically, it is composed of multiple filiform projections, which are thickened and lined with normal-appearing stratified squamous epithelium without any evidence of atypia, dysplasia, or other malignant features. The cells are arranged in an orderly maturation pattern towards the surface, which typically shows abundant keratinization, commonly in the form of parakeratin. Orthokeratin with sparse keratohyalin granules may be present. Parakeratin crypting and plugging may be seen. The advancing front of the tumor is broad and pushing with bulbous rete ridges, which extend deeper than the level of the subjacent normal mucosa but with no evidence of invasion. An intense inflammatory cell infiltrate often precedes the advancing front of the tumor (Fig. 48).

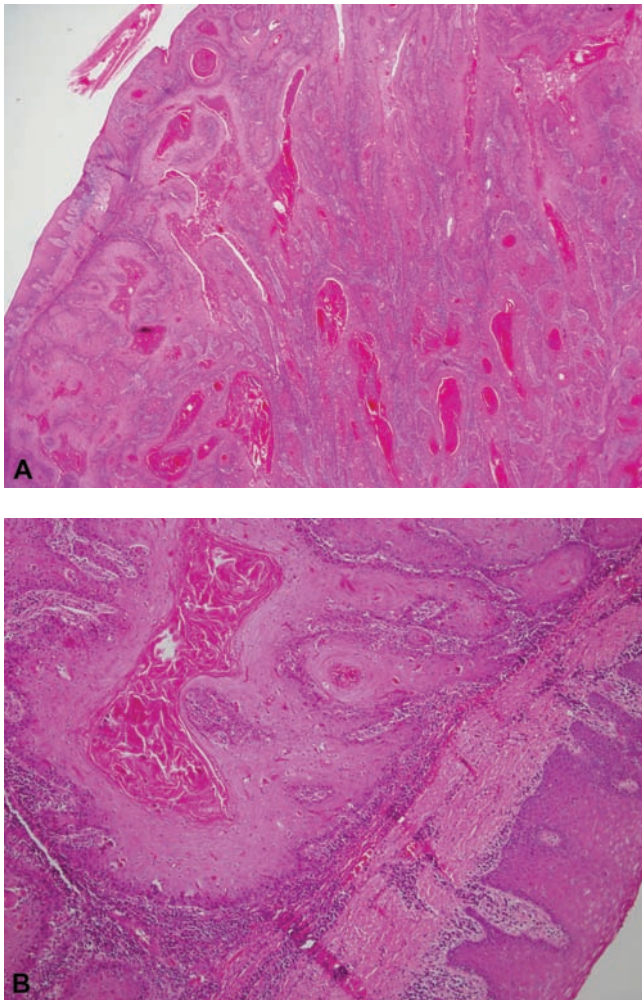


Figure 48 (A) VC advancing below the surface mucosa and showing keratin plugging (20×). (B) Bland squamous epithelium showing normal maturation. Intense chronic inflammatory cell infiltrate is present surrounding stroma (100×). *Abbreviation:* VC, verrucous carcinoma.

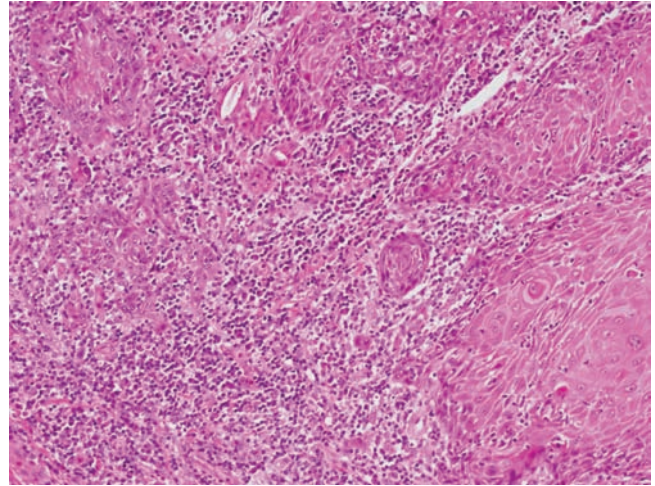


Figure 49 Conventional invasive SCC arising in VC (200×). *Abbreviation:* VC, verrucous carcinoma; SCC, squamous cell carcinoma.

VC differs from conventional SCC not only morphologically, but also molecularly and cytogenetically. Using immunohistochemical techniques, Wu et al. (527) have shown that oral VC showed lower levels of expression of p53 and EGFR than conventional SCC. The difference was statistically significant. A similar relationship was also noted for TGF- α and cyclin D1; however, it was not statistically significant.

In another study, it was shown that expression of cyclin D1 was significant when poorly differentiated SCC was compared with oral VC (528). In VC, cells in S phase of the cell cycle are limited to the basal layer or within three cell layers of the basement membrane. This is in distinct contrast to conventional SCC in which S-phase cells are present in all layers of the epithelium (529). Ogawa et al. (530) reported positive reactivity for the cell-to-cell adhesion molecule CD44v9 in 8 of 10 cases of VC but in only 2 of 10 metastasizing SCCs examined. However, VC can be a precursor to conventional invasive SCC. Medina et al. have called attention to the existence of VCs that contain foci of conventional SCC, which are termed hybrid tumors (531). In their review of 104 cases of VC of the oral cavity, 20 (19.2%) were considered hybrid tumors. This study underscores the need for thorough microscopic sampling of VC for foci of invasive SCC (Fig. 49). Such a discovery implies that the tumor has acquired the ability to metastasize and should be expected to behave as a conventional SCC.

C. Differential Diagnosis

Two lesions that bear some morphologic similarities to VC are considered here: VH (papillary keratosis) and papillary squamous carcinoma. The latter is discussed separately below as a variant of conventional SCC.

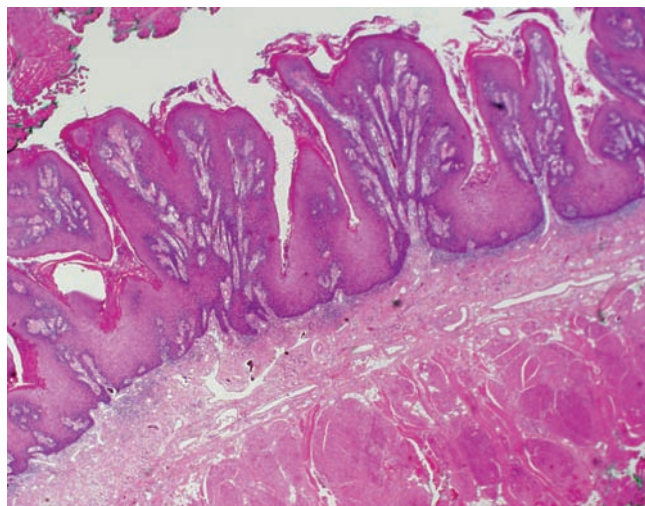


Figure 50 VH. The rete pegs do not extend below the level of adjacent mucosa (100 $\times$). *Abbreviation:* VH, verrucous hyperplasia.

The term “verrucous hyperplasia” was coined by Shear and Pindborg in 1980 to describe an oral mucosal lesion that resembles VC, both clinically and microscopically (532). Microscopically, both VC and VH exhibit exophytic papillary projections that may be hyperkeratinized. The main distinction between the two lesions is that in VH the rete pegs are superficial to, or at least at the same level as, the adjacent mucosa (Fig. 50), whereas in VC they extend deeper into the underlying stroma (532–534).

Whether VH is a distinct lesion, an early VC, or a progenitor of conventional invasive SCC, is controversial (505,525,533,535). VH is not uncommonly found in association with VC and/or conventional SCC (525,532–534,536). The simultaneous or metachronous existence of these three lesions in the same patient is notably encountered in patients with PVL.

Wu et al. have demonstrated that the level of expression of p53 and EGFR in VH is analogous to that of VC and is significantly lower than that of invasive SCC (527). Poh et al. found that the pattern of allelic loss (LOH) in VH is similar to that of VC and differed from conventional SCC (536).

D. Treatment and Prognosis

As discussed above, VC exists within a histologic continuum from premalignant VH to invasive SCC. Distinguishing VC from VH and from lesions with a dominant VC component, which also contain small foci of squamous carcinoma (hybrid tumors) may be difficult, but is essential for the proper assessment of treatment modalities and prediction of outcomes.

In a review of the NCDB, Koch et al. (526) found 2350 cases of VC of the head and neck diagnosed between 1985 and 1996. Sixty percent of these were located in the oral cavity. Surgery alone was the most

frequent single modality, accounting for 77.8% of the oral cases. The most likely sites to be treated with radiation alone were the oropharynx, larynx, and hypopharynx. The two sites most often receiving combined surgery and radiation therapy were the RMT (20.8%) and oropharynx (20%). Stage was also a factor in determining the type of the treatment modality used. Early-stage oral cavity disease was treated by surgery alone in most cases (85.8%). However, patients with advanced disease were less likely to be treated with surgery alone (56.9%). It is of interest that across the years of this study, surgery as a single modality increased from 66.4% in 1985 to 73.7% in 1996.

The common use of surgery as the dominant treatment may reflect concern that irradiation of VC is not only less effective but also more likely to result in anaplastic dedifferentiation resulting in recurrence and more aggressive cancer (531). Resistance to radiotherapy and possible progression to invasive carcinoma was also suggested in review of 148 previously published cases (537). It is noteworthy, however, that more recent work argues against irradiation-induced anaplastic transformation as a viable concern (538,539). Controversy persists regarding the efficacy of irradiation in managing VC. The NCDB identifies worse outcome among the cases treated with irradiation. Markedly better results favor the initial management of oral cavity tumors surgically, with 85.7% five-year survival, as compared with that of irradiation (41.8%) (526). These rates should be interpreted with the understanding that management with irradiation alone is often chosen for patients with extensive cancers, considered “incurable,” and for patients with extensive morbidity precluding surgery.

The contemporary NCDB report represents the patterns of care for VC of the head and neck in the United States. Surgical excision alone is the most common treatment of VC. Improved outcomes were not shown with the addition of radiation therapy to surgery. Initial management with irradiation alone resulted in notable worse survival compared with surgical treatment, for both laryngeal and oral cavity VC. Despite these findings, a definitive statement cannot be made regarding treatment efficacy because of the possibility that unknown selection bias may account for the differences observed (526).

The more rigorous current pathologic practice to exclude hybrid and other variants will likely result in the reporting of improved survival rates for VC.

XV. PAPILLARY SQUAMOUS CARCINOMA

To our knowledge, one of the earliest reports on papillary SCC (PSCC) in the upper aerodigestive tract was published in the first series of the AFIP Atlas of Tumor Pathology, in 1968 (540). Reviewing 39 patients with tonsillar carcinoma who were treated at the Mayo Clinic from 1941 to 1950, Parkhill identified seven patients who had what was described as nonkeratinizing PSCC (540). Microscopically, the tumors were composed of exophytic, filiform, finger-like papillary projections supported with slender

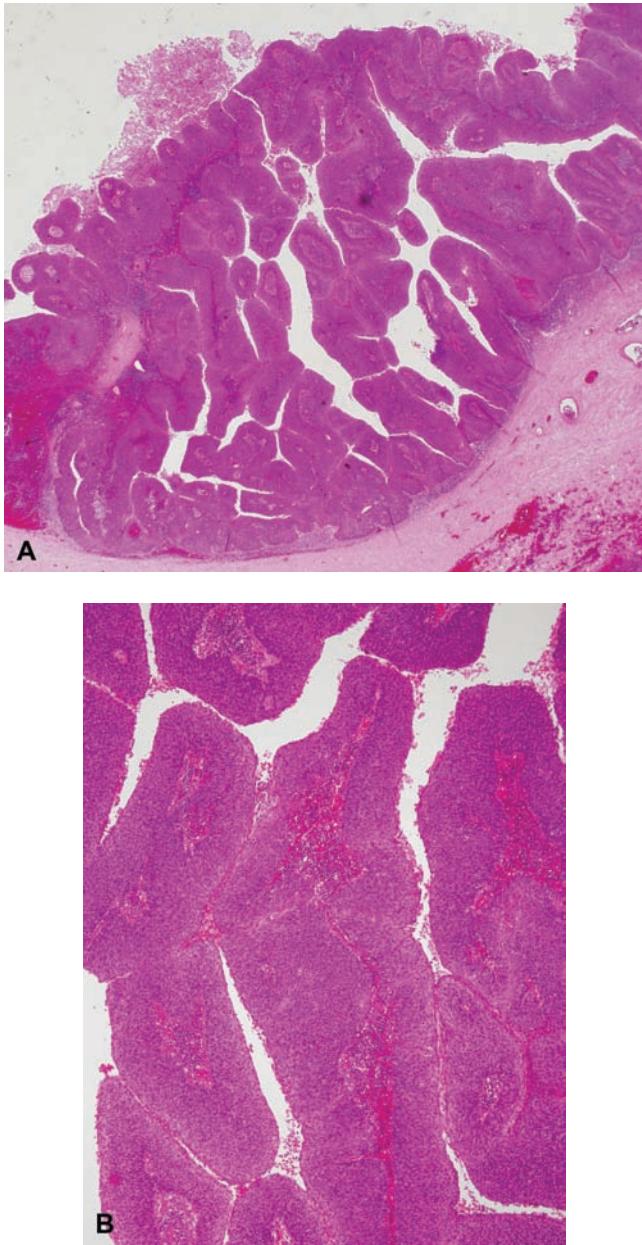


Figure 51 (A) Papillary squamous carcinoma of the tonsils showing slim exophytic filiform finger-like projection (20 $\times$). (B) Higher magnification showing thin papillary projection supported with delicate fibrovascular cores and covered with surface epithelium exhibiting top-to-bottom dysplasia (100 $\times$).

fibrovascular cores (Fig. 51). The surface epithelial cells had dark staining nuclei and scant cytoplasm and lacked keratinization. The tumors were described as resembling transitional cell carcinoma of the urogenital tract. The lesions showed small-to-large proportion of carcinoma in situ. Patients with non-keratinizing papillary squamous carcinoma had much better five-year survival rate (71%) as compared with those with the keratinizing-type carcinomas (30%) (540). However, recognition of PSCC as a distinct

clinicopathologic variant of squamous cell carcinoma has, so far, not been established.

Confusion about the true identity of PSCC arose in the subsequent literature, after its initial description, which resulted from including other exophytic entities of SCC with true papillary squamous carcinoma. In the second edition of the World Health Organization (WHO) *Histological Typing of Tumors of the Upper Respiratory Tract and Ear*, published in 1991, PSCC was not classified separately and the term PSCC was applied to "invasive SCC, which have an exophytic papillary component" (541).

In a review of exophytic squamous neoplasms of the head and neck, Ishiyama et al. (542) described two morphologic variants, which exhibited different architectural growth patterns: (i) an inverting verrucous pattern characterized by prominent keratinization and (ii) an exophytic papillary pattern with little or no keratinization. Verrucous inverting lesions lacking cellular dysplasia were classified separately as VCs and were excluded. Those with cytologic atypia were categorized as papillary squamous neoplasms. These included both of the aforementioned groups: the keratinizing inverting (31 cases) and the exophytic nonkeratinizing papillary (21 cases). The latter is histologically identical to papillary squamous carcinoma, as initially described in the first series of the AFIP Atlas (540). In this study, the most common site for these papillary squamous neoplasms was the oral cavity, particularly the alveolar ridge and buccal mucosa. No distinctions were made on the site specificity of each of the two types.

Thompson et al. (543) reviewed 104 cases of exophytic SCCs and PSCC of the larynx, identified in the AFIP files from 1971 to 1991. Similar to Ishiyama's study mentioned above (542), the tumors were divided according to their growth pattern into broad-based exophytic (92 cases) and papillary-frond (12 cases). The latter consisted of thin, delicate filiform, finger-like papillary projections; the exophytic pattern showed broad-based bulbous projections. All lesions, irrespective of type, demonstrated atypical cytologic features such as nuclear enlargement, loss of cellular polarity, increased nuclear-cytoplasmic ratio and increased mitosis. With an average follow-up of 8.6 years for 87 patients, they reported that 17 patients with an exophytic pattern died of disease, while none of the patients with the papillary pattern did. They concluded that patients with PSCC and exophytic SCCs of the larynx have better prognosis than those with conventional SCC and that the prognosis of those with true PSCCs is even better.

In the most recent WHO classification of tumors of the head and neck, PSCC of the larynx was defined as a variant characterized by a predominant papillary growth pattern, the papillae are covered by neoplastic, immature basaloid cells and supported with thin fibrovascular cores. Keratinization is sparse or absent (444).

The lack of familiarity with the clinicopathologic features of PSCC of the oral cavity and oropharynx may be due to the low incidence of these tumors. More importantly, however, is the imprecision of diagnosis and definition of this type of carcinoma.

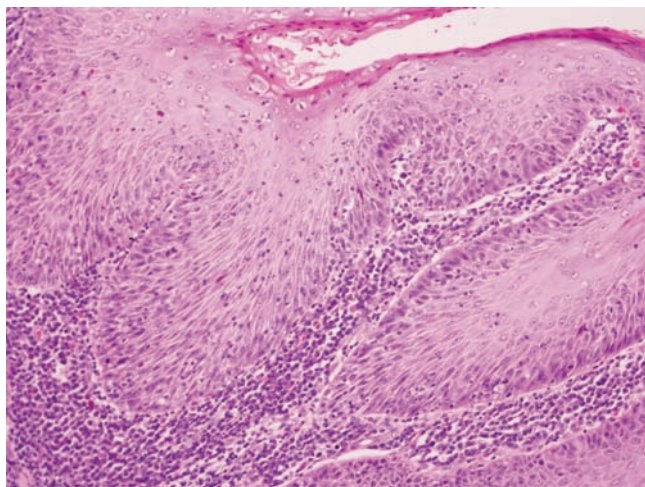


Figure 52 Atypical VH. Notice the dysplastic changes (200 $\times$).
Abbreviation: VH, verrucous hyperplasia.

Currently, reports dealing with PSCC exclude the other exophytic carcinoma (544), which is broad-based with bulbous club-shaped ridges and excessive keratinization and dysplastic cytologic features. Such an entity should be classified as either atypical VH, in the absence of invasion (Fig. 52), or SCC with verrucous features, if invasive elements are identified (Fig. 49).

The term papillary squamous carcinoma should be reserved for those lesions with slender, finger-like exophytic papillae containing delicate fibrovascular cores. The surface epithelium shows full-thickness dysplasia. The epithelial cells have basaloid appearance and frequent mitoses. Surface keratinization is characteristically sparse or absent (Fig. 51). Despite their large size, many of the tumors remain in situ or only show superficial invasion of the lamina propria. In the absence of invasion, the tumor should be termed PSCC in situ (545).

A putative role for HPV in the etiology of PSCC of oral and oropharyngeal cavity is unclear. Suarez et al. (546) using PCR techniques identified HPV in 5 of 14 cases of PSCC of the upper aerodigestive tract. HPV type 16 or 18 in three cases and types 6 of 11 in two. The exact site of the carcinomas was not identified. The tumors were morphologically consistent with the PSCC as described above. More recently, HPV type 16 was identified in PSCC of the tonsil in a renal transplant recipient (547). Crissman et al. (548) showed that PSCC is unrelated to recurrent respiratory papillomatosis. After a long period of follow up, none of the patients with recurrent papillomatosis developed PSCC, and none of the patients with papillary squamous carcinoma had previous history of recurrent respiratory papillomatosis.

A. Treatment and Prognosis

Because of a lack of studies on large series of PSCC of the oral cavity and oropharynx, it is not possible to evaluate the effectiveness of various therapeutic

modalities and to predict prognosis. As alluded to above, PSCC can be predominantly in situ. Lymph nodes are characteristically negative. However, a case of PSCC of the base of tongue was reported in a patient, initially presenting with a large cervical lymph node metastasis (549). From the limited number of cases with follow-up information, it seems possible to conclude that PSCC may have a better prognosis than conventional SCC but a worse outcome than VC.

In a study on cellular proliferation activity in PSCC, VC and conventional SCC, Takeda et al. found that PSCC had considerably higher Ki67-labeling scores than VC. However, there was no significant difference in Ki67 expression among PSCC and conventional SCC (550).

B. Differential Diagnosis

Morphologic differences between PSCC, VC, hybrid verrucous-SCC and atypical VH are detailed in the above discussion. Another lesion that must be distinguished from PSCC is nonkeratinizing squamous papilloma. The latter lacks the full thickness of epithelial dysplasia that characterizes PSCC.

XVI. SPINDLE CELL (SARCOMATOID) CARCINOMA

SpCC (1) is a variant of SCC characterized by spindled or pleomorphic tumor cells, which simulate a true sarcoma. This tumor is one of the most unusual and interesting lesions of the head and neck. Numerous alternate terms, several of which are preferred at other specific body sites, have been used, including metaplastic carcinoma (2), anaplastic carcinoma (3), pleomorphic carcinoma (4), carcinosarcoma, and pseudosarcoma, among others (5,6). These tumors have been described everywhere carcinomas arise, but are most common in the head and neck region, lung, and urinary bladder. Many different theories for their pathogenesis have been put forward in the past, including divergent differentiation of carcinoma cells, so-called collision tumors where there are two separate neoplastic clones combined in the same lesion (5), or that the carcinoma “drives” a non-neoplastic (6) stromal component to proliferate in the same lesion. Over time, from ultrastructural (7–10), immunohistochemical (11–16), and genetic investigations (17,18), it has become abundantly clear that the first theory is correct, namely, that the sarcomatoid tumor represents a line of differentiation or “dedifferentiation” of the carcinoma. Furthermore, there is ample evidence that squamous carcinoma cells can exhibit mesenchymal transformation (19,20). As such, SpCC is regarded as a histologic variant of SCC. The tumor is fundamentally a carcinoma, but is composed, in large part or completely, of spindled or pleomorphic cells, which simulate a sarcoma or other spindle cell neoplasm. Most SpCCs are biphasic tumors, consisting of the spindle cell component and also a typical squamous carcinoma component or at least focal carcinoma in situ. However, a significant number

are composed only of spindled or pleomorphic tumor cells, making them very difficult to recognize as carcinoma.

A. Clinical Features

SpCC has similar demographics to conventional SCC. It is strongly associated with smoking and drinking and, for cases in the oral cavity and oropharynx, has a 2 to 3:1 male-to-female ratio (15,16,21,22). In other head and neck sites, this ratio is skewed much more toward males (10,11,13,22). In most series, it occurs most commonly in the larynx, particularly in the glottis (11), followed by the oral cavity, hypopharynx, and nasal cavity (16,22). Some series, however, have found a higher percentage of cases in the oral cavity and, in particular, in the oropharynx (15). The typical age range is from 55 to 65 years (21,22). A significant minority of patients have a history of previous radiation to the originating site. Combining four major clinicopathologic studies, 17% of the 300 cases of SpCC occurred in a previously irradiated field at an average of seven years and as late as 16 years later (11,14,21,22). This is a much higher rate than for conventional SCC. Oral cavity tumors usually arise in the lip, alveolar ridge, and tongue and present with swelling, pain, a nonhealing ulcer, dysphagia, or hemorrhage (21). A unique clinical and pathologic feature of SpCC is its macroscopic growth pattern. More than 90% of laryngeal tumors (11,15,16) and approximately 50% of oral tumors (21) present as polypoid and exophytic masses projecting into the lumen (Fig. 53). Sometimes there is a narrow stalk.

B. Pathology

The polypoid growth pattern usually results in an exophytic mass with a smooth and extensively ulcerated

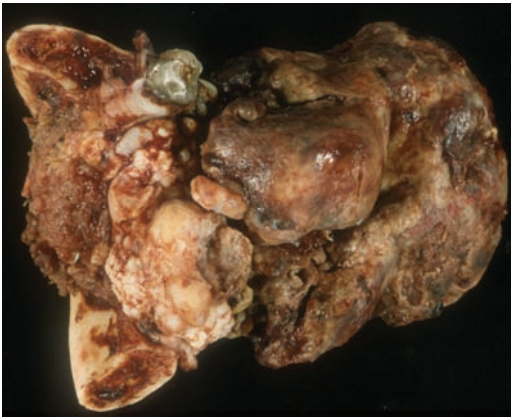


Figure 53 Gross photograph of a resected oral cavity SpCC, which is extensively polypoid and ulcerated. There is hyperkeratotic white thickening of the intact alveolar mucosa, which showed severe squamous dysplasia on histology. *Abbreviation:* SpCC, spindle cell carcinoma.

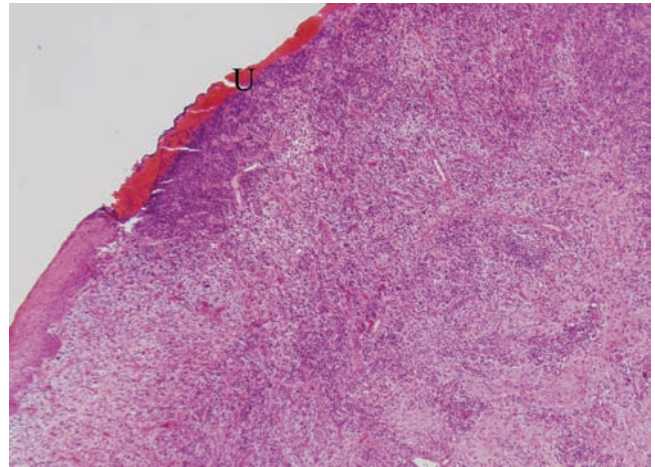


Figure 54 Ulcerated (U) SpCC consisting of a sheet of spindled tumor cells with abundant mixed associated inflammatory cells (40 $\times$). *Abbreviation:* SpCC, spindle cell carcinoma.

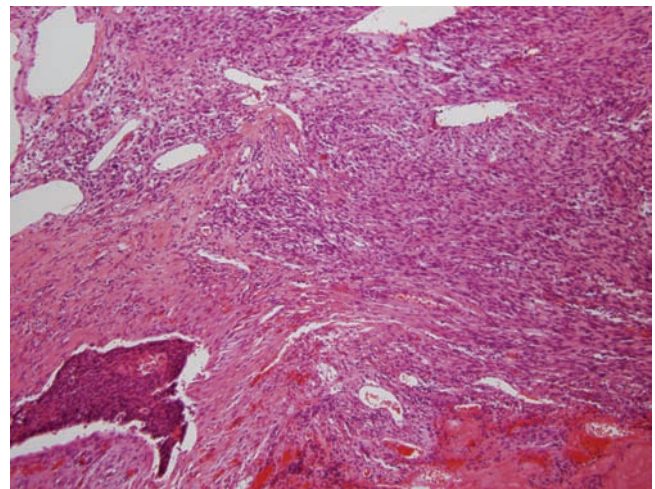


Figure 55 Biphasic SpCC with nests of moderately differentiated SCC intermixed with sheets of fusiform spindle cells with a fascicular growth pattern (100 $\times$). *Abbreviations:* SCC, squamous cell carcinoma; SpCC, spindle cell carcinoma.

surface (Fig. 54). 66 to 75 percent of SpCC are biphasic tumors with areas of conventional SCC admixed with areas of spindled and/or pleomorphic tumor cells (11,12,16) (Fig. 55). The spindled component usually predominates (21). The conventional squamous neoplasia may take the form of squamous dysplasia, carcinoma in situ or invasive carcinoma. Since the tumors are usually exophytic with extensive surface ulceration, this can render a noninvasive component very focal or absent. The spindled cells may be bland and regular or may be markedly pleomorphic with multinucleated giant tumor cells. There may be a wide variety of architectural patterns, including fascicular,

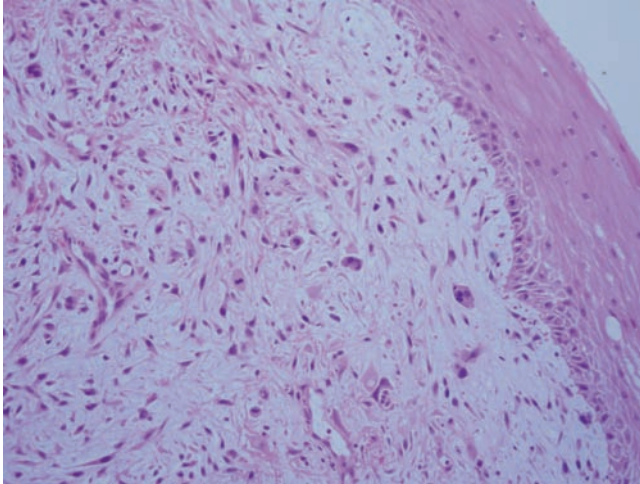


Figure 56 Hypocellular SpCC consisting of markedly atypical spindled, stellate, and pleomorphic tumor cells sitting in an edematous, loose submucosa (200 $\times$). *Abbreviation:* SpCC, spindle cell carcinoma.

storiform, or lace-like (10,21). On occasion, the tumor cells may be widely spaced apart in an edematous and inflamed stroma (Fig. 56), with tumor cells mimicking granulation tissue or reactive soft tissue such as fibroblasts with radiation-related stromal cell atypia. This is a common pitfall for the surgical pathologist, possibly resulting in a benign misdiagnosis.

Approximately 5% of tumors will have definable (heterologous) sarcomatous differentiation, either osteosarcomatous with osteoid production or chondrosarcomatous with cartilage formation (10–12,16,21,22). Rhabdomyosarcomatous differentiation has been reported very rarely (23,24). Finally, another diagnostic pitfall is where the spindle cell component demonstrates loss of cohesion of the tumor cells and consequently mimics an angiosarcoma. This is well described in other body sites as pseudoangiosarcomatous carcinoma (25,26) and also in the oral cavity as pseudovascular carcinoma (27).

Although any malignant spindle cell lesion along the mucosa of the upper aerodigestive tract should be considered a SpCC until proven otherwise, immunohistochemistry is nonetheless very important to confirm the epithelial/carcinomatous nature of the spindle cells. Oral cavity and oropharyngeal SpCC stain exactly like those occurring at other head and neck sites (13,15). Cytokeratins have been extensively studied in the spindle cell component, and they show only variable positivity. Commonly used pancytokeratin (AE1/AE3 with or without CAM 5.2) is positive in 25% to 60% of tumors (10–13,15,16) (Fig. 57). With an extended panel of keratin stains, this number can be modestly increased, up to 68% in the large series (187 laryngeal cases) by Thompson et al. (11) or 85.7% (5/6 cases) in oral cases reported by Takata et al. (28). EMA is positive in 20% to 45% of cases (11,15,16). This leaves a significant minority of cases without evidence of epithelial differentiation by hematoxylin and eosin (H&E) or

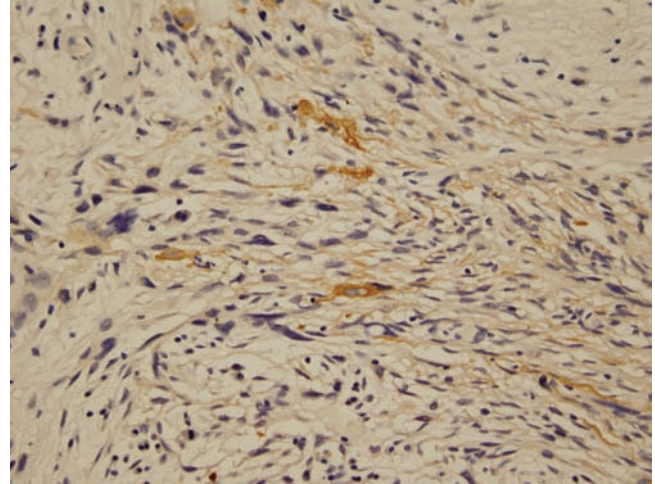


Figure 57 Focal positive cytokeratin immunostaining in the spindle cell (sarcomatoid) component of a SpCC (400 $\times$). *Abbreviation:* SpCC, spindle cell carcinoma.

traditional immunohistochemistry. Immunostaining for p63, another marker of epithelial differentiation, which is positive in the basal layer cells of normal squamous epithelium, is positive in approximately two-thirds of cases, including a significant number where cytokeratin is negative (15) (Fig. 58). It retains the high specificity for carcinomas just like the cytokeratins, so is also useful in diagnosis. Virtually 100% of cases are positive for vimentin with strong staining (10–13,16). There is also evidence of specific mesenchymal proteins with smooth muscle actin staining in approximately 30% of cases, muscle-specific actin in approximately 10% to 15%, and desmin in approximately 2% to 5% (11).

Ultrastructural examination of SpCC shows cytoplasmic tonofilament bundles and tonofilament-associated desmosomes in the spindle cells, features associated with epithelial differentiation (7–10).

When a conventional SCC component is present intermingled with the spindle cells, the diagnosis of SpCC is confirmed without the need for additional studies. This can take the form of squamous dysplasia, carcinoma in situ, or frankly invasive carcinoma. When the lesion is purely spindled or pleomorphic cells, one must first decide if it is malignant. SpCC can appear deceptively bland with regular, fusiform spindle cells in fascicles (Fig. 59) or loosely embedded in a very hypocellular and edematous stroma with numerous small vessels and with or without an associated inflammatory infiltrate. The former pattern can mimic a number of benign or low-grade spindle cell neoplasms. The latter pattern, particularly given the penchant for these tumors to present as polypoid and ulcerated masses, can very closely mimic benign granulation tissue (Fig. 60). This is a serious challenge for the surgical pathologist, particularly at the time of frozen section. One must look closely to identify and recognize the atypical spindle cells. Cutting additional

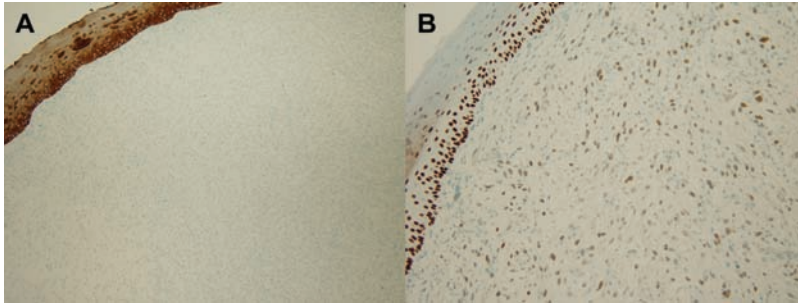


Figure 58 Immunohistochemistry for p63 (**B**), which is positive in SpCC, while the corresponding pancytokeratin immunohistochemistry (**A**) is negative (200× for each panel). *Abbreviation:* SpCC, spindle cell carcinoma.

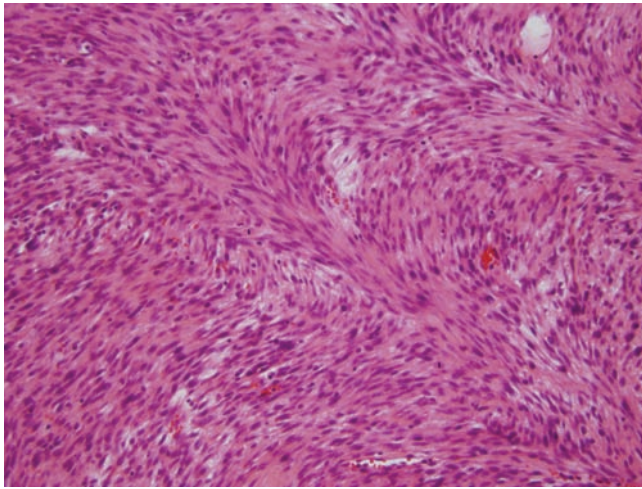


Figure 59 SpCC showing bland spindle cells with relatively abundant eosinophilic cytoplasm and growing in fascicles (200×). *Abbreviation:* SpCC, spindle cell carcinoma.

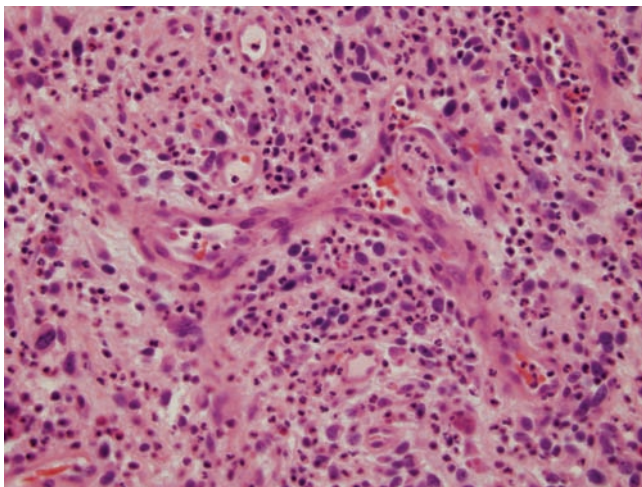


Figure 60 Markedly inflamed SpCC mimicking granulation tissue. The tumor cells are rounded and atypical and sit in a loose, edematous stroma surrounded by mixed inflammatory cells and with abundant intermixed capillaries with plump endothelial cells (400×). *Abbreviation:* SpCC, spindle cell carcinoma.

sections of the tumor or deeper levels often will demonstrate a conventional carcinoma component (21). If this fails, then the differential diagnosis becomes quite broad, including myriad spindle cell lesions, most notably benign lesions such as nodular fasciitis, inflammatory myofibroblastic tumor, inflammatory pseudotumor, and sinonasal polyps with stromal atypia and malignant lesions such as angiosarcoma, fibrosarcoma, melanoma, synovial sarcoma, or leiomyosarcoma. Truly recognizing the malignant nature of the spindle cells by morphology and using epithelial marker immunostains will differentiate SpCC from those benign lesions.

Fortunately, true sarcomas are exceedingly uncommon along the head and neck mucosa, such that, when faced with a malignant-appearing spindle cell neoplasm at these sites, it is statistically more likely a SpCC. Cytokeratin and p63 immunostains will rule all of these other entities out with the exception of angiosarcoma and synovial sarcoma (15,29). Muscle markers such as smooth muscle actin and muscle-specific actin can be positive in SpCC (11), so one cannot rely on them in this differential. Angiosarcomas occur infrequently in the oral cavity and may be exophytic just as SpCC (30). The vascular markers CD31 and CD34 will be positive in angiosarcoma (30–32) and are not expressed by SpCC (11,27). Synovial sarcoma is probably the most difficult to differentiate (33). It may present as a polypoid or sessile mucosal mass with a similar histologic appearance and will stain with epithelial markers (29). Subtle morphology and molecular analysis for the t(X;18) translocation characteristic of synovial sarcoma may be necessary.

C. Treatment and Prognosis

Since SpCC is inherently a carcinoma, current treatment recommendations are essentially identical to those for conventional squamous carcinoma. But just as with the histogenesis, terminology, and morphology of SpCC, the prognosis is also somewhat a complex and controversial topic. If one looks at all patients and all sites together, the prognosis does not appear different from conventional SCC (14). However, this does not tell the whole story. Critical to prognosis is the location of the tumor. Tumors of the oral cavity act aggressively (6,21,22,34,35). Tumors of the larynx, particularly the glottis, do much better than those of the

oral cavity, hypopharynx, oropharynx, and sinonasal region (6,11,14,22). As with conventional squamous carcinoma, the depth of tumor invasion is important, but this seems accentuated in SpCC such that minimally invasive tumors do very well and those with any significant degree of invasion do worse than conventional squamous carcinoma of the same stage (22,35). Interestingly, polypoid conformation, by itself, does not confer a better prognosis (11,14,21), presumably because the degree of invasion beneath the polyp is the critical factor. Finally, and curiously and for unknown reasons, lack of keratin immunoreactivity in the spindle cells also has been correlated with a better prognosis (11,14).

XVII. NEUROENDOCRINE CARCINOMA

Neuroendocrine carcinomas of the head and neck are relatively rare, and when they do occur, it is predominantly in the larynx (1,2). Oral cavity and oropharyngeal neuroendocrine carcinomas are quite uncommon, with approximately 20 cases reported in the literature. Neuroendocrine carcinomas of the head and neck, just as in the lung, are broadly classified into three categories: carcinoid tumor (low grade or well-differentiated neuroendocrine carcinoma), atypical carcinoid tumor (intermediate grade or moderately differentiated neuroendocrine carcinoma), and small cell carcinoma (high grade or poorly differentiated neuroendocrine carcinoma – HGNEC). The latter group also includes rare HGNEC with large cells with generous eosinophilic cytoplasm (large cell neuroendocrine carcinoma). All reported cases of primary oral neuroendocrine carcinoma have been HGNEC, and they frequently have an intermixed component of SCC. True carcinoid tumors have not been reported in the oral cavity or oropharynx. As a final general point, many authors have referred to oral cavity HGNEC as Merkel cell carcinoma, which is the term traditionally reserved for HGNEC of the skin (3,7,12). As the oral mucosa develops from ectoderm just as the skin does, Merkel cell carcinomas certainly could feasibly occur in the mouth. However, while there may well be phenotypically different neuroendocrine carcinomas in the oral cavity, to date, the literature does not clearly distinguish them. For purposes of this discussion, they will all be considered together.

A. Clinical Features

The overwhelming majority of oral cavity and oropharyngeal neuroendocrine carcinomas occur in men (3,4,5,6). Beyond this, the small number of cases does not allow for broad generalization of the clinical features. Of the reported cases, the majority have been in the oral cavity with a few reported in the oropharynx (3,4,5,6,7,8). Specific oral sites include the lip (3,14,7), FOM (12), RMT (6), tongue (3), and alveolar ridges (4,13). There is no significant difference in tumors among these subsites. Almost all of the patients are heavy smokers (8). Presenting symptoms include mouth pain, bleeding, or a neck mass.

B. Pathology

The gross findings are not distinct. Masses usually are bulging and ulcerated but, where not ulcerated, are usually somewhat smooth-surfaced. Tumors may have a component of SCC. These mixed tumors are usually more granular and ragged in appearance. Microscopically, there are poorly circumscribed sheets, cords, and nests of small blue undifferentiated tumor cells (Fig. 61). The cells have very little cytoplasm, and their nuclei range from round and regular to more angulated and fusiform. There is frequently significant chromatin crush artifact. The cells that are preserved display nuclear molding and have a chromatin that is finely stippled or granular (Fig. 62). Nucleoli, if present, are small and inconspicuous (3,10,15). There is very brisk mitotic activity, abundant apoptosis, and usually areas of necrosis. Rarely, tumors will have cells with more cytoplasm, rosette-like structures, and peripheral palisading. Tumors with these features have been classified, in other organ sites, as large cell neuroendocrine carcinoma (5,9).

Immunohistochemistry is positive for pan cytokeratin, usually with a characteristic, punctate, or dot-like, perinuclear pattern (Fig. 63). The reactivity may be limited or focal in some cases. Since only a portion of the reported cases have been stained for cytokeratin 20, full conclusions cannot be made. Certainly, some of the cases are positive for that marker (3,7). Neuroendocrine stains such as synaptophysin and chromogranin A are positive in most cases, but reactivity may be limited (3,4,5,6,7). The tumors are negative for S-100 and leukocyte common antigen and are usually negative for high molecular weight cytokeratins. Ultrastructurally, there are rare membrane-bound, dense core neurosecretory granules (5,10) and occasional cell junctions.

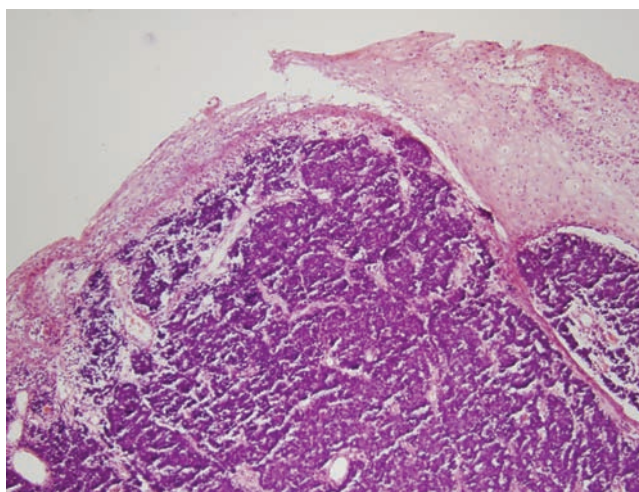


Figure 61 Low-power view of high-grade neuroendocrine carcinoma of the oral cavity showing sheets of small, blue cell tumor in the submucosa (100 $\times$).

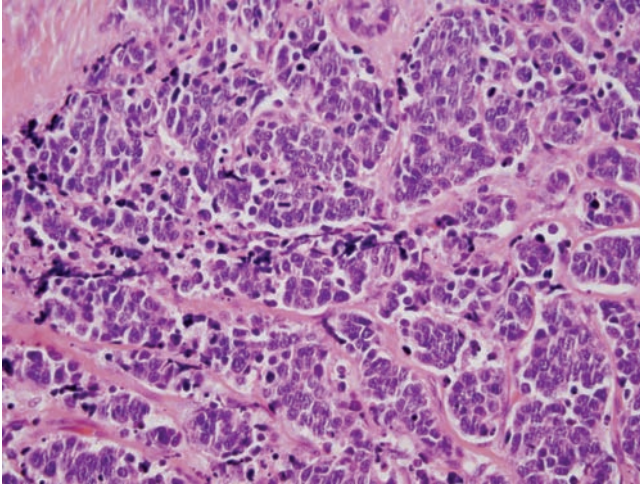


Figure 62 High-power view of high-grade neuroendocrine carcinoma of the oral cavity. The tumor consists of sheets and nests of small, blue cells with granular “salt and pepper” chromatin, little cytoplasm, and brisk mitotic activity with abundant apoptosis (400 $\times$).

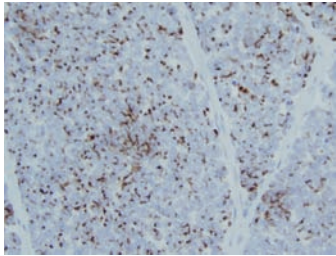


Figure 63 Cytokeratin immunohistochemistry in high-grade neuroendocrine carcinoma showing punctate, dot-like positive staining in the tumor cells (400 $\times$).

The differential diagnosis includes a number of tumors with a “blue-cell” appearance, including poorly differentiated SCC, lymphoma, BSC, solid-type (grade III) ACC, melanoma, and Ewing’s sarcoma. The punctate cytoplasmic pattern of cytokeratin reactivity is one of the most reliable diagnostic features of neuroendocrine differentiation, followed by immunohistochemistry for synaptophysin, chromogranin A, or CD56 (N-CAM). The distinction from BSC and solid-type ACC may be assisted by strong immunostaining for these tumors with high molecular weight cytokeratins such as 34 β E12 and CK 5/6, which are usually negative in neuroendocrine carcinomas (16,17). Also, although uncommon, metastatic small cell carcinoma, particularly from the lung, must be considered (18,19) and ruled out clinically. Although TTF-1 immunostaining is a specific marker of pulmonary carcinomas of other types, it is positive in a significant minority of nonpulmonary small cell

carcinomas (11), so cannot be relied upon to diagnose metastasis from the lung.

C. Treatment and Prognosis

HGNEC is an extremely aggressive neoplasm. The majority of patients [more than 70% (8)] develop metastatic disease to cervical lymph nodes and also distantly to the liver, lungs, brain, or bones. Approximately one-third have nodal disease at presentation, and most patients develop cervical nodal disease or local recurrence within the first year (3,4,5,6). Widespread metastatic disease is common (3) with spread to the liver, bones, and brain (3,4,8). Because these are such aggressive tumors, which have a very high rate of distant failure, nonsurgical therapy has been recommended (8). Surgical resection of the primary tumor is performed only if it is of very low morbidity or for the very rare case of a well or moderately differentiated neuroendocrine carcinoma (8). If surgical therapy is undertaken, neck dissection is recommended even in the absence of clinical nodal disease. Aggressive induction chemotherapy, akin to that used for pulmonary small cell carcinoma, is used followed by definitive radiation therapy (3,8). Two-thirds of the reported patients with oral cavity or oropharyngeal HGNEC have died of disease within one to two years.

XVIII. ORAL MALIGNANT MELANOMA

Mucosal melanoma is a neoplasm composed of melanocytes or melanocytic precursors, which, perhaps to the surprise of some, is not particularly uncommon in the oral cavity. Interestingly, oral mucosa has the same density of melanocytes as some skin sites (1,2), although it is not normally pigmented, except in darker-skinned individuals (3). Pigmentation does occur in response to local trauma, systemic medications, or related to race—the darker a person’s skin, the more likely they are to have a pigmented lesion (3). Also, benign melanocytic lesions such as melanotic macule, melanoacanthoma, true melanocytic nevi, or the rare melanotic neuroectodermal tumor of infancy do occur, rarely, in the oral cavity (4–8). While the head and neck is a common site in general for melanomas (up to 30% of all cases), most of which are cutaneous and ocular (9), the oral cavity and oropharynx represent the primary site for less than 1% of melanomas across the board (1) and approximately 0.5% of all cancers (1,10) in the oral cavity. 50 to 60 percent of all mucosal melanomas occur in the head and neck (11), divided roughly equally between the oral cavity and the nasal cavity/paranasal sinuses (1,9). While the incidence of cutaneous melanomas is markedly increasing (12), particularly in the Caucasian population, the incidence of mucosal melanomas is only gradually increasing (9,13). The reason for this difference may be that, unlike cutaneous melanoma, where there is a strong relationship with sun exposure and actinic damage, no such relationship exists for mucosal melanomas (9). In fact, no etiologic factors have been

ascertained for these lesions. Although a number of benign oral melanocytic lesions occur, there are only very rare examples that have progressed to malignant melanoma (14,15). For this reason, and because of the small numbers of benign oral melanocytic lesions, the risk of their transformation to melanoma is unclear (16).

A. Clinical Features

Oral melanoma occurs in adults with an average age of approximately 60 years (1,9,17–19), but there is a roughly even incidence from age 20 to 80 years (1). Oral melanoma is very rare in children (17). There is a slight male predominance with 60% occurring in men (13,17). Unlike in cutaneous melanoma, where the vast majority of patients are Caucasian, oral melanomas occur in dark-skinned individuals with relative frequency (9). In a review of 93 patients, Chaudhry et al. (20) reported 22% occurring in dark-skinned races. Three distinct clinical presentations and pathways are recognized (21): The first is as an incidental, asymptomatic, pigmented lesion noted by a dentist or physician. The second, seen in approximately one-third of patients, is the patient noting a flat, pigmented lesion, which remains present for months to years before they seek attention or before an actual mass develops (17,20,22). The remaining patients present with a recently developing mass. Patients complain of pain, ulceration, bleeding, or loose teeth (1). The most common oral site is the hard palate (~40%) followed by the maxillary alveolar ridge (~25%) and then the buccal mucosa, mandibular gingiva, and lip. Rare cases occur in the tongue, FOM, and oropharynx (1,17,19,23). Clinically, the lesions are heterogeneous with colors ranging from black to gray to purple or red (Fig. 64). There can be intermixed white areas, which may represent foci of regression (1,19). The flatter lesions are irregular in outline. Nodular masses may or may not be pigmented or ulcerated, and sometimes satellite nodules can be seen (19) without intervening pigmentation.



Figure 64 Clinical photograph showing a patient with melanoma of the maxillary alveolus and upper lip.

B. Pathology

Just as with the clinical appearance, resected melanomas grossly consist of variably pigmented black or gray, macular or nodular lesions ranging from 1.5 to 4 cm. Eighty-five percent of tumors demonstrate melanin pigment (1) so the cut surface is frequently dark-colored to black. Histologically, oral melanomas show identical features to cutaneous lesions. They can be in situ or invasive. However, unlike in the skin, the vast majority of oral melanomas (85%) are deeply invasive at presentation (1). Most invasive tumors (~2/3) also still have an in situ component as well (1,19), which consists of atypical melanocytes with clear cytoplasm sitting singly or, less commonly, in nests, along the basal layer of the epithelium. This typically leads to a “rarified” or vacuolated appearance. These cells have scattered intracytoplasmic melanin and nuclei which are round to oval and hyperchromatic or have vesicular chromatin with prominent nucleoli (19) (Fig. 65). Occasionally, in situ melanoma can be seen involving seromucinous glands. There is frequently upward migration of single melanocytes in the epithelium, but nests above the interface are quite uncommon, and mitoses are scarce. In invasive tumors, cells invade the submucosa singly and in sheets, clusters, or islands and are either epithelioid, spindled, or a mixture of both types. Epithelioid cells are more common and have round contours with eosinophilic to gray cytoplasm and central round nuclei with vesicular chromatin and prominent “cherry red” nucleoli (Fig. 66). Intranuclear cytoplasmic inclusions, although commonly described in cutaneous and ocular melanomas, are only infrequently encountered in oral melanoma. Occasional tumors may have plasmacytoid cells (1,19,24). In tumors with mixed cell types, the spindle cell component is usually minor or focal. Pure spindle cell lesions are least common (25). These

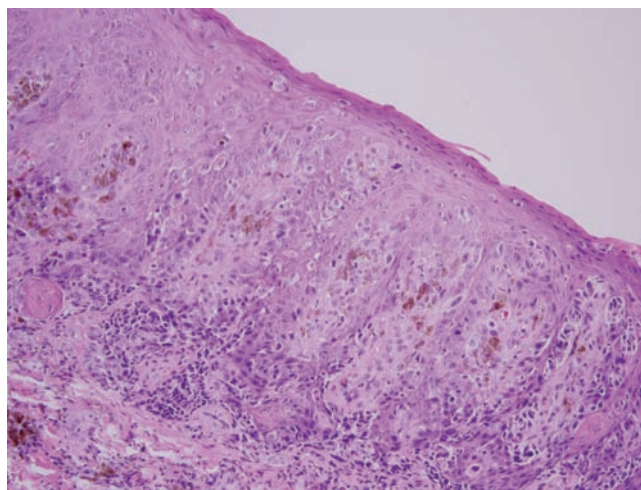


Figure 65 Melanoma in situ of the hard palate showing a confluent proliferation of atypical melanocytes along the basal layer along with many single cells in the upper epithelium (pagetoid spread) (200×).

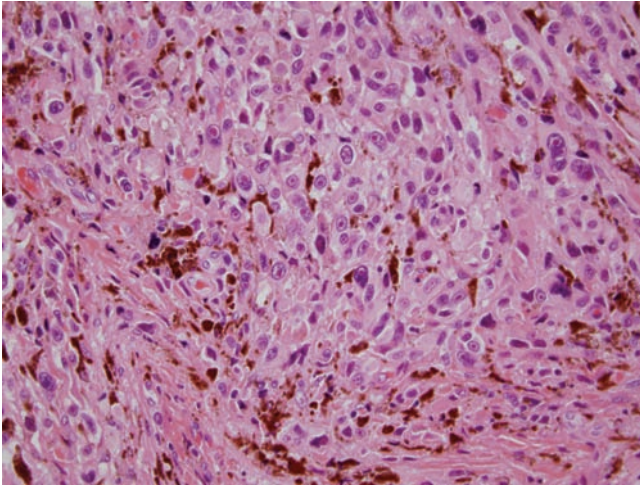


Figure 66 Epithelioid malignant melanoma consisting of sheets of rounded tumor cells with prominent eosinophilic cytoplasm and central, round nuclei with vesicular chromatin and prominent, eosinophilic nucleoli. There is prominent melanin pigment (400 $\times$).

consist of sheets of fusiform cells with oval to cigar-shaped nuclei and cytoplasm which varies from eosinophilic to clear (Fig. 67). Desmoplastic-type melanomas with a dense collagenous background and more elongated nuclei have been rarely described, most of which are nonpigmented and demonstrate perineural invasion (19,26–30). When considered as a whole, nuclear pleomorphism and mitotic activity in oral melanomas range from minimal to marked, but frank necrosis is not commonly seen. Finally, more than 90% of tumors contain melanin pigment that can be seen on microscopic examination (17,19).

Melanomas of the oral cavity do not fit particularly well into the classification scheme for cutaneous melanomas (1,17,31). Early attempts to classify oral melanomas in this way led to tumors being described as lentigo maligna melanoma (LMM) (32) and others as being of the acral lentiginous pattern/type (31,33–35). Those lacking an in situ component resemble nodular melanoma. Because no pattern has been associated with a specific behavior or prognostic difference, it has been proposed that these terms not be used (22). Instead, oral melanomas with an in situ

component may simply be termed “oral melanoma with radial growth phase” (17) or as more recently proposed the varying lesions should be termed simply as “in situ melanoma,” “invasive melanoma,” or “invasive melanoma with an in situ component” (19). Borderline lesions may be termed “atypical melanocytic proliferation” (1,15,19).

Most oral melanomas are deeply invasive at presentation. The great majority have a Breslow thickness of greater than 4 mm (36), with none of the cases in a large review by Hicks et al. less than 1.5 millimeters (1). For this reason, Breslow thickness measurements have not proven prognostic in oral cavity melanomas and need not be reported. By immunohistochemistry, 90% to 97% of tumors are positive for S-100 protein (25,37), but this cell marker lacks specificity. Melan-A (or MART-1) and tyrosinase are much more specific for melanoma, and expression is present in almost 100% of cases of epithelioid melanoma. However, a few cases of spindle cell melanoma and many cases of desmoplastic melanoma are negative. HMB-45 and microphthalmia transcription factor-1 are positive in approximately 75% (25) of melanomas as well.

Melanoma is notorious for its mimicry of other types of neoplasms. Since the vast majority of oral melanomas are pigmented, it is important to look for melanin, which is quite specific for melanoma. The differential diagnosis for epithelioid melanoma includes poorly differentiated or undifferentiated carcinoma, rhabdoid tumor, and plasmacytoma. For spindle cell melanoma, the differential includes sarcomatoid carcinoma and myriad soft tissue-type tumors such as malignant peripheral nerve sheath tumor. Positive immunohistochemistry for S-100 and at least one of the more specific melanoma markers such as melan-A, tyrosinase, or HMB-45 is key to the diagnosis. Most importantly, metastatic melanoma must be ruled out. Virtually all patients with metastatic melanoma to the oral cavity will have a history of a previous primary lesion elsewhere, most will be amelanotic as opposed to primary oral melanomas, and all lack an in situ component (38).

C. Treatment and Prognosis

The prognosis for oral and oropharyngeal melanomas is poor. Numerous studies examining this have demonstrated a collective five-year survival between 15% and 25% (1,4,9,17,20,21,39–41) with one series showing

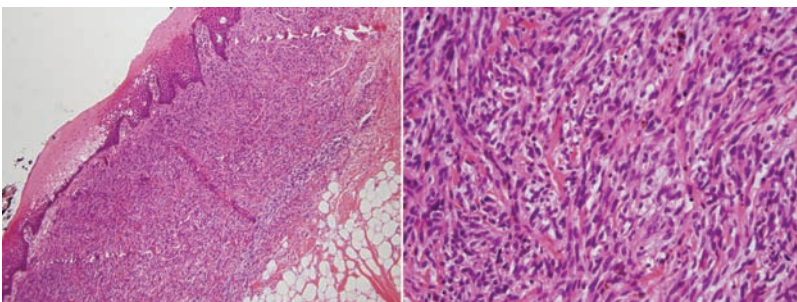


Figure 67 Spindle cell melanoma showing sheets of regular spindle cells in the submucosa (*left*), which, on higher power, show fusiform nuclei, inconspicuous nucleoli, and moderate amounts of eosinophilic to clear cytoplasm (*right*). There is focal melanin pigment (100 $\times$ *left* and 400 $\times$ *right*).

40% survival (42). There is slight variation by site, with alveolar ridge lesions doing slightly better than palatal (1,9) and oropharyngeal ones. Although one might suspect that tumors with an in situ component or preexisting pigmented lesion present before the mass-forming invasive tumor forms might show a better behavior, this has not been demonstrated (32). Tumor spreads to cervical lymph nodes in approximately 40% of cases (41), and this appears to confer a worse prognosis with shorter disease-specific survival (19,24,36,41). Distant metastases usually occur after several years, are often seen in the lungs, liver, and brain, and are almost always associated with recurrent disease at the primary site (42).

Treatment consists of radical surgery, but local recurrence is very common (31–85%) (18). As some patients have prolonged survival despite multiple recurrences, aggressive treatment is still recommended when it recurs (40). Selective neck dissection is performed for clinically detected cervical metastases. Elective neck dissection is controversial but is generally not performed. Radiotherapy and systemic therapy are used in most cases, but there is no consensus on the types, regimens, or their efficacy.

REFERENCES

- Neville BW, Damm DD, Allen CM, et al. Oral and maxillofacial pathology. In: Neville BW, Damm DD, Allen CM et al., eds. *Epithelial Pathology*. 2nd ed. Philadelphia: WB Saunders, 2002:356–366.
- Batsakis JG. Oral cancer. In: Shah JP, Johnson NW, Batsakis JG, eds. *Clinical Pathology of Oral Cancer*. London: Martin Dunitz, an imprint of the Taylor & Francis Group, 2002.
- Agency for Research on Cancer (IARC). Available at: <http://www.dep.iarc.fr/>. IARC. 2006.
- Johnson N. Tobacco use and oral cancer: a global perspective. *J Dent Educ* 2001; 65(4):328–339.
- Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001; 2(9):533–543.
- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007; 57(1):43–66.
- Mao L, Hong WK, Papadimitrakopoulou VA. Focus on head and neck cancer. *Cancer Cell* 2004; 5(4):311–316.
- Mashberg A, Samit A. Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. *CA Cancer J Clin* 1995; 45(6):328–351.
- Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. *Cancer* 2005; 103(9):1843–1849.
- Frisch M, Hjalgrim H, Jaeger AB, et al. Changing patterns of tonsillar squamous cell carcinoma in the United States. *Cancer Causes Control* 2000; 11(6):489–495.
- Neville BW, Day TA. Oral cancer and precancerous lesions. *CA Cancer J Clin* 2002; 52(4):195–215.
- Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988; 48(11):3282–3287.
- Wey PD, Lotz MJ, Friedman LJ. Oral cancer in women nonusers of tobacco and alcohol. *Cancer* 1987; 60(7):1644–1650.
- Rahman M, Fukui T. Bidi smoking and health. *Public Health* 2000; 114(2):123–127.
- Gupta PC, Mehta FS, Pindborg JJ. Mortality among reverse chutta smokers in south India. *Br Med J (Clin Res Ed)* 1984; 289(6449):865–866.
- Gupta PC, Warnakulasuriya S. Global epidemiology of areca nut usage. *Addict Biol* 2002; 7(1):77–83.
- van Wyk CW, Stander I, Padayachee A, et al. The areca nut chewing habit and oral squamous cell carcinoma in South African Indians. A retrospective study. *S Afr Med J* 1993; 83(6):425–429.
- Warnakulasuriya KA. Analytical studies of the evaluation of the role of the betel quid in oral carcinogenesis. In: Bedi Red. *Betel Quid and Tobacco Chewing Among the Bangladeshi Community in the United Kingdom*. London: Center for Transcultural Oral Health, 1995.
- Balaran P, Sridhar H, Rajkumar T, et al. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *Int J Cancer* 2002; 98(3):440–445.
- Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. *Respirology* 2003; 8(4):419–431.
- Bhide S, Kulkarni JR, Padma PR, et al. Studies on tobacco specific nitrosamines and other carcinogenic agents in smokeless tobacco products. In: Sanghvi LD, Notany PP, eds. *Tobacco and Health: the Indian Scene*. Proceedings of the IICC Workshop. Bombay: Tata Memorial Center, 1989:121–131.
- Brown RL, Suh JM, Scarborough JE, et al. Snuff Dippers' Intraoral Cancer: clinical Characteristics and Response to Therapy. *Cancer* 1965; 18:2–13.
- McCoy JM, Waldron CA. Verrucous carcinoma of the oral cavity. A review of forty-nine cases. *Oral Surg Oral Med Oral Pathol* 1981; 52(6):623–629.
- Winn DM, Blot WJ, Shy CM, et al. Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med* 1981; 304(13):745–749.
- Krishnamurthy S, Ramaswamy R, Trivedi U, et al. Tobacco use in rural Indian children. *Indian Pediatr* 1997; 34(10):923–927.
- IARC. Tobacco Smoking; 1986.
- Lafuente A, Maristany M, Arias C, et al. Glutathione and glutathione S-transferases in human squamous cell carcinomas of the larynx and GSTM1 dependent risk. *Anticancer Res* 1998; 18(1A):107–111.
- Rodriguez T, Altieri A, Chatenoud L, et al. Risk factors for oral and pharyngeal cancer in young adults. *Oral Oncol* 2004; 40(2):207–213.
- Kato I, Nomura AM. Alcohol in the aetiology of upper aerodigestive tract cancer. *Eur J Cancer B Oral Oncol* 1994; 30B(2):75–81.
- IARC. Alcohol drinking. IARC Working Group, Lyon, 13–20 October 1987. IARC Monogr Eval Carcinog Risks Hum 1988; 44:1–378.
- Hindle J. The epidemiology of oral cancer in England and Wales, 1901–1991. University of London PhD thesis, 1997.
- Moller H. Changing incidence of cancer of the tongue, oral cavity, and pharynx in Denmark. *J Oral Pathol Med* 1989; 18(4):224–229.
- Andre K, Schraub S, Mercier M, et al. Role of alcohol and tobacco in the aetiology of head and neck cancer: a case-control study in the Doubs region of France. *Eur J Cancer B Oral Oncol* 1995; 31B(5):301–309.
- Bundgaard T, Wildt J, Frydenberg M, et al. Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control* 1995; 6(1):57–67.
- Franceschi S, Talamini R, Barra S, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. *Cancer Res* 1990; 50(20):6502–6507.
- Zheng TZ, Boyle P, Hu HF, et al. Tobacco smoking, alcohol consumption, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. *Cancer Causes Control* 1990; 1(2):173–179.

37. Weaver A, Fleming SM, Smith DB. Mouthwash and oral cancer: carcinogen or coincidence? *J Oral Surg* 1979; 37(4): 250–253.
38. Cole P, Rodu B, Mathisen A. Alcohol-containing mouthwash and oropharyngeal cancer: a review of the epidemiology. *J Am Dent Assoc* 2003; 134(8):1079–1087.
39. Mascarenhas AK, Allen CM, Loudon J. The association between Viadent use and oral leukoplakia. *Epidemiology* 2001; 12(6):741–743.
40. Mascarenhas AK, Allen CM, Moeschberger ML. The association between Viadent use and oral leukoplakia—results of a matched case-control study. *J Public Health Dent* 2002; 62(3):158–162.
41. Blum HF. Sunlight as a causal factor in cancer of the skin of man. *J Natl Cancer Inst* 1948; 9:247–258.
42. Blum HF. Sunlight as an environmental factor in cancer of the skin. *Mil Med* 1955; 117(3):202–208.
43. Decker J, Goldstein JC. Risk factors in head and neck cancer. *N Engl J Med* 1982; 306(19):1151–1155.
44. Keller AZ. Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. *Am J Epidemiol* 1970; 91(5):486–499.
45. Spitzer WO, Hill GB, Chambers LW, et al. The occupation of fishing as a risk factor in cancer of the lip. *N Engl J Med* 1975; 293(9):419–424.
46. Tan KN. Cancer of the lip in Australia. *Aust Dent J* 1970; 15(3):179–184.
47. Shpitzer T, Stern Y, Segal K, et al. Carcinoma of the lip: observations on its frequency in females. *J Laryngol Otol* 1991; 105(8):640–642.
48. Blomqvist G, Hirsch JM, Alberius P. Association between development of lower lip cancer and tobacco habit. *J Oral Maxillofac Surg* 1991; 49:1044–1047.
49. Broders AC. Squamous cell epithelioma of the lip. *J Am Med Assoc* 1920; 74(10):656–664.
50. Widmann BP. Cancer of the lip. *Am J Roentgenol* 1950; 63(1):13–25.
51. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007; 356(19):1944–1956.
52. El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: a distinct clinicopathologic and molecular disease entity. *Am J Surg Pathol* 2003; 27(11):1463–1470.
53. El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. *Am J Surg Pathol* 2005; 29(10):1367–1372.
54. El-Mofty SK, Patil S. Human papillomavirus (HPV)-related oropharyngeal nonkeratinizing squamous cell carcinoma: characterization of a distinct phenotype. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 101(3):339–345.
55. Franceschi S, Munoz N, Bosch XF, et al. Human papillomavirus and cancers of the upper aerodigestive tract: a review of epidemiological and experimental evidence. *Cancer Epidemiol Biomarkers Prev* 1996; 5(7):567–575.
56. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000; 92(9):709–720.
57. Mork J, Lie AK, Glatte E, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2001; 344(15):1125–1131.
58. Brennan JA, Boyle JO, Koch WM, et al. Association between cigarette smoking and mutation of the p53 gene in squamous-cell carcinoma of the head and neck. *N Engl J Med* 1995; 332(11):712–717.
59. Regezi JA, Sciubba J. *Oral Pathology—Clinical-pathological correlations*. 2nd ed. Philadelphia: WB Saunders, 1993.
60. Velly AM, Franco EL, Schlecht N, et al. Relationship between dental factors and risk of upper aerodigestive tract cancer. *Oral Oncol* 1998; 34(4):284–291.
61. Stix G. A malignant flame. *Sci Am* 2007; 297(1):60–68.
62. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 2006; 6(1):24–37.
63. Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 2005; 7(3):211–217.
64. Lewis CE, Pollard JW. Distinct role of macrophages in different tumor microenvironments. *Cancer Res* 2006; 66(2):605–612.
65. Eisenberg E, Krutchkoff DJ. Lichenoid lesions of oral mucosa. Diagnostic criteria and their importance in the alleged relationship to oral cancer. *Oral Surg Oral Med Oral Pathol* 1992; 73(6):699–704.
66. Rindum JL, Stenderup A, Holmstrup P. Identification of *Candida albicans* types related to healthy and pathological oral mucosa. *J Oral Pathol Med* 1994; 23(9):406–412.
67. Krogh P, Hald B, Holmstrup P. Possible mycological etiology of oral mucosal cancer: catalytic potential of infecting *Candida albicans* and other yeasts in production of N-nitrosobenzylmethylamine. *Carcinogenesis* 1987; 8(10): 1543–1548.
68. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. *Nutr Cancer* 1992; 18(1):1–29.
69. La Vecchia C, Tavani A, Franceschi S, et al. Epidemiology and prevention of oral cancer. *Oral Oncol* 1997; 33(5): 302–312.
70. Potter JD, Steinmetz K. Vegetables, fruit and phytoestrogens as preventive agents. *IARC Sci Publ* 1996; (139):61–90.
71. Prime SS, MacDonald DG, Rennie JS. The effect of iron deficiency on experimental oral carcinogenesis in the rat. *Br J Cancer* 1983; 47(3):413–418.
72. Zheng T, Boyle P, Willett WC, et al. A case-control study of oral cancer in Beijing, People's Republic of China. Associations with nutrient intakes, foods and food groups. *Eur J Cancer B Oral Oncol* 1993; 29B(1):45–55.
73. Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; 370(9581):59–67.
74. King GN, Healy CM, Glover MT, et al. Increased prevalence of dysplastic and malignant lip lesions in renal-transplant recipients. *N Engl J Med* 1995; 332(16): 1052–1057.
75. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. *JAMA* 2006; 296(23):2823–2831.
76. Hunter KD, Parkinson EK, Harrison PR. Profiling early head and neck cancer. *Nat Rev Cancer* 2005; 5(2):127–135.
77. Jefferies S, Foulkes WD. Genetic mechanisms in squamous cell carcinoma of the head and neck. *Oral Oncol* 2001; 37(2):115–126.
78. Reed AL, Califano J, Cairns P, et al. High frequency of p16 (CDKN2/MTS-1/INK4A) inactivation in head and neck squamous cell carcinoma. *Cancer Res* 1996; 56(16): 3630–3633.
79. Izzo JG, Papadimitrakopoulou VA, Liu DD, et al. Cyclin D1 genotype, response to biochemoprevention, and progression rate to upper aerodigestive tract cancer. *J Natl Cancer Inst* 2003; 95(3):198–205.
80. Patturajan M, Nomoto S, Sommer M, et al. DeltaNp63 induces beta-catenin nuclear accumulation and signaling. *Cancer Cell* 2002; 1(4):369–379.

81. Lippman SM, Sudbo J, Hong WK. Oral cancer prevention and the evolution of molecular-targeted drug development. *J Clin Oncol* 2005; 23(2):346–356.
82. Prime SS, Thakker NS, Pring M, et al. A review of inherited cancer syndromes and their relevance to oral squamous cell carcinoma. *Oral Oncol* 2001; 37(1):1–16.
83. Cheng L, Sturgis EM, Eicher SA, et al. Glutathione-S-transferase polymorphisms and risk of squamous-cell carcinoma of the head and neck. *Int J Cancer* 1999; 84(3):220–224.
84. Sturgis EM, Wei Q. Genetic susceptibility—molecular epidemiology of head and neck cancer. *Curr Opin Oncol* 2002; 14(3):310–317.
85. Chen XS, Garcea RL, Goldberg I, et al. Structure of small virus-like particles assembled from the L1 protein of human papillomavirus 16. *Mol Cell* 2000; 5(3):557–567.
86. Lukaszuk K, Liss J, Wozniak I, et al. HPV and histological status of pelvic lymph node metastases in cervical cancer: a prospective study. *J Clin Pathol* 2004; 57(5):472–476.
87. Syrjanen SM, Syrjanen KJ. New concepts on the role of human papillomavirus in cell cycle regulation. *Ann Med* 1999; 31(3):175–187.
88. zur Hausen H. Molecular pathogenesis of cancer of the cervix and its causation by specific human papillomavirus types. *Curr Top Microbiol Immunol* 1994; 186:131–156.
89. AJCC. Cancer Staging Manual. 6th ed. New York: Springer, 2002.
90. Broder AC. The grading of carcinoma. *Minn Med* 1925; 8:726.
91. Bryne M, Koppang HS, Lilleng R, et al. New malignancy grading is a better prognostic indicator than Broders' grading in oral squamous cell carcinomas. *J Oral Pathol Med* 1989; 18(8):432–437.
92. Bryne M, Koppang HS, Lilleng R, et al. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. *J Pathol* 1992; 166(4):375–381.
93. Bryne M, Nielsen K, Koppang HS, et al. Reproducibility of two malignancy grading systems with reportedly prognostic value for oral cancer patients. *J Oral Pathol Med* 1991; 20(8):369–372.
94. Sawair FA, Irwin CR, Gordon DJ, et al. Invasive front grading: reliability and usefulness in the management of oral squamous cell carcinoma. *J Oral Pathol Med* 2003; 32(1):1–9.
95. Odell EW, Jani P, Sherriff M, et al. The prognostic value of individual histologic grading parameters in small lingual squamous cell carcinomas. The importance of the pattern of invasion. *Cancer* 1994; 74(3):789–794.
96. Riffko J. Prognostic value of histopathological factors (malignancy grading and AgNOR content) assessed at the invasive tumor front of oral squamous cell carcinoma. *Br J Cancer* 1997; 75:1543–1546.
97. Kurokawa H, Zhang M, Matsumoto S, et al. The relationship of the histologic grade at the deep invasive front and the expression of Ki-67 antigen and p53 protein in oral squamous cell carcinoma. *J Oral Pathol Med* 2005; 34(10):602–607.
98. Tumuluri V, Thomas GA, Fraser IS. Analysis of the Ki-67 antigen at the invasive tumour front of human oral squamous cell carcinoma. *J Oral Pathol Med* 2002; 31(10):598–604.
99. Brown B, Barnes L, Mazariegos J, et al. Prognostic factors in mobile tongue and FOM carcinoma. *Cancer* 1989; 64(6):1195–1202.
100. Shingaki S, Suzuki I, Kobayashi T, et al. Predicting factors for distant metastases in head and neck carcinomas: an analysis of 103 patients with locoregional control. *J Oral Maxillofac Surg* 1996; 54(7):853–857.
101. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. *Head Neck* 1995; 17(6):463–472.
102. O'Brien CJ, Lauer CS, Fredricks S, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness? *Head Neck* 2003; 25(11):937–945.
103. Po Wing Yuen A, Lam KY, Lam LK, et al. Prognostic factors of clinically stages I and II oral tongue carcinoma—A comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez-Gimeno score, and pathologic features. *Head Neck* 2002; 24(6):513–520.
104. Yuen AP, Lam KY, Wei WI, et al. A comparison of the prognostic significance of tumor diameter, length, width, thickness, area, volume, and clinicopathological features of oral tongue carcinoma. *Am J Surg* 2000; 180(2):139–143.
105. Jones KR, Lodge-Rigal RD, Reddick RL, et al. Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. *Arch Otolaryngol Head Neck Surg* 1992; 118(5):483–485.
106. Urist MM, O'Brien CJ, Soong SJ, et al. Squamous cell carcinoma of the buccal mucosa: analysis of prognostic factors. *Am J Surg* 1987; 154(4):411–414.
107. Mohit-Tabatabai MA, Sobel HJ, Rush BF, et al. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. *Am J Surg* 1986; 152(4):351–353.
108. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg* 1986; 152(4):345–350.
109. Anderson DL. Cause and prevention of lip cancer. *J Can Dent Assoc (Tor)* 1971; 37(4):138–142.
110. Hornback NB, Shidnia H. Carcinoma of the lower lip: treatment results at Indiana University Hospitals. *Cancer* 1978; 41(1):352–357.
111. Keller AZ. The epidemiology of lip, oral, and pharyngeal cancers, and the association with selected systemic diseases. *Am J Public Health Nations Health* 1963; 53:1214–1228.
112. Lindqvist C, Teppo L. Epidemiological evaluation of sunlight as a risk factor of lip cancer. *Br J Cancer* 1978; 37(6):983–989.
113. Chen J, Katz RV, Krutchkoff DJ, et al. Lip cancer. Incidence trends in Connecticut, 1935–1985. *Cancer* 1992; 70(8):2025–2030.
114. NIH. Management Guidelines for Head and Neck Cancer: U.S. Department of Health, Education, and Welfare. National Institute of Health.; 197x.
115. Rice D. General management guidelines. In: *Current Concepts in Head and Neck Cancer*. Atlanta: American Cancer Society, 1989:1–15.
116. Baker SR, Krause CJ. Carcinoma of the lip. *Laryngoscope* 1980; 90(1):19–27.
117. Cruse CW, Radocha RF. Squamous cell carcinoma of the lip. *Plast Reconstr Surg* 1987; 80(6):787–791.
118. Brandwein-Gensler M, Teixeira MS, Lewis CM, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol* 2005; 29(2):167–178.
119. Cross J. Carcinoma of the lip: A review of 563 case records of carcinoma of the lip at the Bondville Hospital. *Surg Gynecol Obstet* 1948; 87:153–162.
120. Frierson HF Jr., Cooper PH. Prognostic factors in squamous cell carcinoma of the lower lip. *Hum Pathol* 1986; 17(4):346–354.
121. Mackay EN, Sellers AH. A statistical review of carcinoma of the lip. *Can Med Assoc J* 1964; 90:670–672.
122. Jorgensen K, Elbrond O, Andersen AP. Carcinoma of the lip. A series of 869 cases. *Acta Radiol Ther Phys Biol* 1973; 12(3):177–190.

123. Ward JE, Hendrick JW. Results of treatment of carcinoma of the lip. *Surgery* 1950; 27:321-342.
124. Zitsch RP III, Park CW, Renner GJ, et al. Outcome analysis for lip carcinoma. *Otolaryngol Head Neck Surg* 1995; 113(5):589-596.
125. Yonkers AJ, Yarrington CT Jr. Cancer of the lip. *Laryngoscope* 1972; 82(4):625-630.
126. Pindborg J. *Oral Cancer and Pre-cancer*. Bristol: John Wright & Sons, 1980:20-32.
127. Lynch GA. Cancer of the lip. *Ulster Med J* 1967; 36(1):44-50.
128. Solomon LM, Rosenthal I, Klapman M. Tumor of lower lip. *Arch Dermatol* 1970; 101(2):241-244.
129. Ballantyne AJ, McCarten AB, Ibanez ML. The extension of cancer of the head and neck through peripheral nerves. *Am J Surg* 1963; 106:651-667.
130. Banerjee TK, Gottschalk PG. Unusual manifestations of multiple cranial nerve palsies and mandibular metastasis in a patient with squamous cell carcinoma of the lip. *Cancer* 1984; 53(2):346-348.
131. Brown RG, Poole MD, Calamel PM, et al. Advanced and recurrent squamous carcinoma of the lower lip. *Am J Surg* 1976; 132(4):492-497.
132. Byers RM, O'Brien J, Waxler J. The therapeutic and prognostic implications of nerve invasion in cancer of the lower lip. *Int J Radiat Oncol Biol Phys* 1978; 4(3-4):215-217.
133. Dodd GD, Dolan PA, Ballantyne AJ, et al. The dissemination of tumors of the head and neck via the cranial nerves. *Radiol Clin North Am* 1970; 8(3):445-461.
134. Laine FJ, Braun IF, Jensen ME, et al. Perineural tumor extension through the foramen ovale: evaluation with MR imaging. *Radiology* 1990; 174(1):65-71.
135. Petrovich Z, Kuisk H, Tobochnik N, et al. Carcinoma of the lip. *Arch Otolaryngol* 1979; 105(4):187-191.
136. Bordin GM, Weitzner S. Distant cutaneous metastases in a patient with squamous-cell carcinoma of the lip. *Oral Surg Oral Med Oral Pathol* 1972; 34(3):445-449.
137. Cerezo L, Liu FF, Tsang R, et al. Squamous cell carcinoma of the lip: analysis of the Princess Margaret Hospital experience. *Radiother Oncol* 1993; 28(2):142-147.
138. de Visscher JG, Botke G, Schakenraad JA, et al. A comparison of results after radiotherapy and surgery for stage I squamous cell carcinoma of the lower lip. *Head Neck* 1999; 21(6):526-530.
139. de Visscher JG, Grond AJ, Botke G, et al. Results of radiotherapy for squamous cell carcinoma of the vermilion border of the lower lip. A retrospective analysis of 108 patients. *Radiother Oncol* 1996; 39(1):9-14.
140. Jesse RH. Extensive cancer of the lip. *Surgical therapy*. *Arch Surg* 1967; 94(4):509-516.
141. Luce EA. Carcinoma of the lower lip. *Surg Clin North Am* 1986; 66(1):3-11.
142. Anderson C, Krutchkoff D, Ludwig M. Carcinoma of the lower lip with perineural extension to the middle cranial fossa. *Oral Surg Oral Med Oral Pathol* 1990; 69(5):614-618.
143. Califano L, Zupi A, Massari PS, et al. Lymph-node metastasis in squamous cell carcinoma of the lip. A retrospective analysis of 105 cases. *Int J Oral Maxillofac Surg* 1994; 23(6 pt 1):351-355.
144. Vartanian JG, Carvalho AL, de Araujo Filho MJ, et al. Predictive factors and distribution of lymph node metastasis in lip cancer patients and their implications on the treatment of the neck. *Oral Oncol* 2004; 40(2):223-227.
145. Bloom ND, Spiro RH. Carcinoma of the cheek mucosa. A retrospective analysis. *Am J Surg* 1980; 140(4):556-559.
146. Hirata RM, Jaques DA, Chambers RG, et al. Carcinoma of the oral cavity. An analysis of 478 cases. *Ann Surg* 1975; 182(2):98-103.
147. Tiecke RW, Bernier JL. Statistical and morphological analysis of four hundred and one cases of intraoral squamous cell carcinoma. *J Am Dent Assoc* 1954; 49(6): 684-698.
148. Rao DN, Ganesh B, Rao RS, et al. Risk assessment of tobacco, alcohol and diet in oral cancer—a case-control study. *Int J Cancer* 1994; 58(4):469-473.
149. Ghoshal S, Mallick I, Panda N, Sharma SC. Carcinoma of the buccal mucosa: analysis of clinical presentation, outcome and prognostic factors. *Oral Oncol* 2006; 42(5):533-539.
150. Conley J, Sadoyama JA. Squamous cell cancer of the buccal mucosa. A review of 90 cases. *Arch Otolaryngol* 1973; 97(4):330-333.
151. Vegers JW, Snow GB, van der Waal I. Squamous cell carcinoma of the buccal mucosa. A review of 85 cases. *Arch Otolaryngol* 1979; 105(4):192-195.
152. Mishra RC, Singh DN, Mishra TK. Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. *Eur J Surg Oncol* 1996; 22(5):502-504.
153. Rosenfeld L, Callaway J. Snuff Dipper's Cancer. *Am J Surg* 1963; 106:840-844.
154. Strome SE, To W, Strawderman M, et al. Squamous cell carcinoma of the buccal mucosa. *Otolaryngol Head Neck Surg* 1999; 120(3):375-379.
155. Chhetri DK, Rawnsley JD, Calcaterra TC. Carcinoma of the buccal mucosa. *Otolaryngol Head Neck Surg* 2000; 123(5):566-571.
156. Martin H, Pflueger OH. *Arch Surg* 1935; 30:731-747.
157. Nair MK, Sankaranarayanan R, Padmanabhan TK. Evaluation of the role of radiotherapy in the management of carcinoma of the buccal mucosa. *Cancer* 1988; 61(7):1326-1331.
158. Dhawan IK, Verma K, Khazanchi RK, et al. Carcinoma of buccal mucosa: incidence of regional lymph node involvement. *Indian J Cancer* 1993; 30(4):176-180.
159. Bahadur S, Chatterjee TK. Chemotherapy in buccal mucosa cancer. *J Surg Oncol* 1986; 32(4):245-247.
160. Dhawan IK, Thakur NS, Madan NC, et al. Polychemotherapy in squamous cell carcinoma of the buccal mucosa. *Cancer* 1983; 51(5):773-777.
161. Tichler T, Ramon Y, Rath P, et al. Neoadjuvant chemotherapy in early-stage and locally advanced small bulk squamous cell carcinoma of the oral cavity and oropharynx. *Isr J Med Sci* 1988; 24(9-10):539-544.
162. Pop LA, Eijkenboom WM, de Boer MF, et al. Evaluation of treatment results of squamous cell carcinoma of the buccal mucosa. *Int J Radiat Oncol Biol Phys* 1989; 16(2):483-487.
163. Cernea P, Billet J. Epithelioma of the buccal mucosa: study of 60 cases. *Rev Stomatol* 1962; 63:222-232.
164. O'Brien PH. Cancer of the cheek (mucosa). *Cancer* 1965; 18(11):1392-1398.
165. Funk GF, Karnell LH, Robinson RA, et al. Presentation, treatment, and outcome of oral cavity cancer: a National Cancer Data Base report. *Head Neck* 2002; 24(2):165-180.
166. Barasch A, Morse DE, Krutchkoff DJ, et al. Smoking, gender, and age as risk factors for site-specific intraoral squamous cell carcinoma. A case-series analysis. *Cancer* 1994; 73(3):509-513.
167. Krolls SO, Hoffman S. Squamous cell carcinoma of the oral soft tissues: a statistical analysis of 14,253 cases by age, sex, and race of patients. *J Am Dent Assoc* 1976; 92(3):571-574.
168. Arosarena O MM, Haug R. Special Considerations with floor of mouth and tongue cancer. *Oral Maxillofac Surg Clin North Am* 2006; 18:521-531.
169. Crissman JD, Gluckman J, Whiteley J, et al. Squamous-cell carcinoma of the floor of the mouth. *Head Neck Surg* 1980; 3(1):2-7.
170. Jin YT, Myers J, Tsai ST, et al. Genetic alterations in oral squamous cell carcinoma of young adults. *Oral Oncol* 1999; 35(3):251-256.

171. Koch WM, Lango M, Sewell D, et al. Head and neck cancer in nonsmokers: a distinct clinical and molecular entity. *Laryngoscope* 1999; 109(10):1544-1551.
172. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people—a comprehensive literature review. *Oral Oncol* 2001; 37(5):401-418.
173. Kuriakose M, Sankaranarayanan M, Nair MK, et al. Comparison of oral squamous cell carcinoma in younger and older patients in India. *Eur J Cancer B Oral Oncol* 1992; 28B(2):113-120.
174. Aksu G, Karadeniz A, Saynak M, et al. Treatment results and prognostic factors in oral tongue cancer: analysis of 80 patients. *Int J Oral Maxillofac Surg* 2006; 35(6):506-513.
175. Sessions DG, Spector GJ, Lenox J, et al. Analysis of treatment results for floor-of-mouth cancer. *Laryngoscope* 2000; 110(10 pt 1):1764-1772.
176. Atula S, Grenman R, Laippala P, et al. Cancer of the tongue in patients younger than 40 years. A distinct entity? *Arch Otolaryngol Head Neck Surg* 1996; 122(12):1313-1319.
177. Bell RB, Kademani D, Homer L, et al. Tongue cancer: is there a difference in survival compared with other subsites in the oral cavity? *J Oral Maxillofac Surg* 2007; 65(2):229-236.
178. Myers JN, Elkins T, Roberts D, et al. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. *Otolaryngol Head Neck Surg* 2000; 122(1):44-51.
179. Carvalho AL, Nishimoto IN, Califano JA, et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer* 2005; 114(5):806-816.
180. Easson EC, Palmer MK. Prognostic factors in oral cancer. *Clin Oncol* 1976; 2(3):191-202.
181. Ildstad ST, Bigelow ME, Remensnyder JP. Intra-oral cancer at the Massachusetts General Hospital. Squamous cell carcinoma of the floor of the mouth. *Ann Surg* 1983; 197(1):34-41.
182. Shaha AR, Spiro RH, Shah JP, et al. Squamous carcinoma of the floor of the mouth. *Am J Surg* 1984; 148(4):455-459.
183. Davidson BJ, Root WA, Trock BJ. Age and survival from squamous cell carcinoma of the oral tongue. *Head Neck* 2001; 23(4):273-279.
184. Pitman KT, Johnson JT, Wagner RL, et al. Cancer of the tongue in patients less than forty. *Head Neck* 2000; 22(3):297-302.
185. Popovtzer A, Shpitzer T, Bahar G, et al. Squamous cell carcinoma of the oral tongue in young patients. *Laryngoscope* 2004; 114(5):915-917.
186. Vargas H, Pitman KT, Johnson JT, et al. More aggressive behavior of squamous cell carcinoma of the anterior tongue in young women. *Laryngoscope* 2000; 110(10 pt 1):1623-1626.
187. Veness MJ, Morgan GJ, Sathiyaseelan Y, et al. Anterior tongue cancer: age is not a predictor of outcome and should not alter treatment. *ANZ J Surg* 2003; 73(11):899-904.
188. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. *Cancer* 1975; 36(3):1021-1028.
189. Applebaum EL, Callins WP, Bytell DE. Carcinoma of the floor of the mouth. *Arch Otolaryngol* 1980; 106(7):419-421.
190. Nason RW, Sako K, Beecroft WA, et al. Surgical management of squamous cell carcinoma of the floor of the mouth. *Am J Surg* 1989; 158(4):292-296.
191. Shaw HJ, Hardingham M. Cancer of the floor of the mouth: surgical management. *J Laryngol Otol* 1977; 91(6):467-488.
192. Ballard BR, Suess GR, Pickren JW, et al. Squamous-cell carcinoma of the floor of the mouth. *Oral Surg Oral Med Oral Pathol* 1978; 45(4):568-579.
193. Mashberg A, Meyers H. Anatomical site and size of 222 early asymptomatic oral squamous cell carcinomas: a continuing prospective study of oral cancer. II. *Cancer* 1976; 37(5):2149-2157.
194. Correa JN, Bosch A, Marcial VA. Carcinoma of the floor of the mouth. Review of clinical factors and results of treatment. *Am J Roentgenol Radium Ther Nucl Med* 1967; 99(2):302-312.
195. Harrold CC Jr. Management of cancer of the floor of the mouth. *Am J Surg* 1971; 122(4):487-493.
196. Kolson H, Spiro RH, Rosewit B, et al. Epidermoid carcinoma of the floor of the mouth. Analysis of 108 cases. *Arch Otolaryngol* 1971; 93(3):280-283.
197. Cuffari L, Tesseroli de Siqueira JT, Nemr K, Rapaport A. Pain complaint as the first symptom of oral cancer: a descriptive study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102(1):56-61.
198. Gorsky M, Epstein JB, Oakley C, et al. Carcinoma of the tongue: a case series analysis of clinical presentation, risk factors, staging, and outcome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; 98(5):546-552.
199. Decroix Y, Ghossein NA. Experience of the Curie Institute in treatment of cancer of the mobile tongue: I. Treatment policies and result. *Cancer* 1981; 47(3):496-502.
200. Hicks WL Jr., Loree TR, Garcia RI, et al. Squamous cell carcinoma of the floor of mouth: a 20-year review. *Head Neck* 1997; 19(5):400-405.
201. Marks JE, Lee F, Freeman RB, et al. Carcinoma of the oral tongue: a study of patient selection and treatment results. *Laryngoscope* 1981; 91(9 pt 1):1548-1559.
202. Decroix Y, Ghossein NA. Experience of the Curie Institute in treatment of cancer of the mobile tongue: II. Management of the neck nodes. *Cancer* 1981; 47(3):503-508.
203. White D, Byers RM. What is the preferred initial method of treatment for squamous carcinoma of the tongue? *Am J Surg* 1980; 140(4):553-555.
204. Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer* 1972; 29(6):1446-1449.
205. Nakissa N, Hornback NB, Shidnia H, et al. Carcinoma of the floor of the mouth. *Cancer* 1978; 42(6):2914-2919.
206. Feind CR, Cole RM. Cancer of the floor of the mouth and its lymphatic spread. *Am J Surg* 1968; 116(4):482-486.
207. McGuirt WF Jr., Johnson JT, Myers EN, et al. Floor of mouth carcinoma. The management of the clinically negative neck. *Arch Otolaryngol Head Neck Surg* 1995; 121(3): 278-282.
208. Shingaki S, Suzuki I, Nakajima T, et al. Evaluation of histopathologic parameters in predicting cervical lymph node metastasis of oral and oropharyngeal carcinomas. *Oral Surg Oral Med Oral Pathol* 1988; 66(6):683-688.
209. Kotwall C, Sako K, Razack MS, et al. Metastatic patterns in squamous cell cancer of the head and neck. *Am J Surg* 1987; 154(4):439-442.
210. Bhattacharyya N, Nayak VK. Survival outcomes for second primary head and neck cancer: a matched analysis. *Otolaryngol Head Neck Surg* 2005; 132(1):63-68.
211. Cianfriglia F, Di Gregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. *Oral Oncol* 1999; 35(2):157-163.
212. Merks MA, van Gulick JJ, Marres HA, et al. Effectiveness of routine follow-up of patients treated for T1-N0 oral squamous cell carcinomas of the floor of mouth and tongue. *Head Neck* 2006; 28(1):1-7.
213. Haughey BH, Gates GA, Arfken CL, et al. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. *Ann Otol Rhinol Laryngol* 1992; 101(2 pt 1):105-112.
214. Brown JS, Griffith JE, Phelps PD, et al. A comparison of different imaging modalities and direct inspection after

- periosteal stripping in predicting the invasion of the mandible by oral squamous cell carcinoma. *Br J Oral Maxillofac Surg* 1994; 32(6):347-359.
215. Shaha AR. Preoperative evaluation of the mandible in patients with carcinoma of the floor of mouth. *Head Neck* 1991; 13(5):398-402.
 216. Soderholm AL, Lindqvist C, Hietanen J, et al. Bone scanning for evaluating mandibular bone extension of oral squamous cell carcinoma. *J Oral Maxillofac Surg* 1990; 48(3):252-257.
 217. Campbell RS, Baker E, Chippindale AJ, et al. MRI T staging of squamous cell carcinoma of the oral cavity: radiological-pathological correlation. *Clin Radiol* 1995; 50(8):533-540.
 218. Virapongse C, Mancuso A, Fitzsimmons J. Value of magnetic resonance imaging in assessing bone destruction in head and neck lesions. *Laryngoscope* 1986; 96(3):284-291.
 219. Segal R. Imaging of malignant neoplasms of the oral cavity. *Br J Radiol (congr Suppl)* 1994; 67:127.
 220. Alvi A ME, Johnson J. *Cancer of the Oral Cavity*. 3rd ed. WB Saunders, 1996.
 221. Jesse RH, BarkleyHTJr., Lindberg RD, et al. Cancer of the oral cavity. Is elective neck dissection beneficial? *Am J Surg* 1970; 120(4):505-508.
 222. Spiro RH, Strong EW. Epidermoid carcinoma of the mobile tongue. Treatment by partial glossectomy alone. *Am J Surg* 1971; 122(6):707-710.
 223. Yco MS, Cruickshank JC. Treatment of stage I carcinoma of the anterior floor of the mouth. *Arch Otolaryngol Head Neck Surg* 1986; 112(10):1085-1089.
 224. Fan KH, Lin CY, Kang CJ, et al. Combined-modality treatment for advanced oral tongue squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2007; 67(2):453-461.
 225. Menezes MB, Lehn CN, Goncalves AJ. Epidemiological and histopathological data and E-cadherin-like prognostic factors in early carcinomas of the tongue and floor of mouth. *Oral Oncol* 2007; 43(7):656-661.
 226. O'Brien CJ, Lahr CJ, Soong SJ, et al. Surgical treatment of early-stage carcinoma of the oral tongue—wound adjuvant treatment be beneficial? *Head Neck Surg* 1986; 8(6):401-408.
 227. Shah JP, Cendon RA, Farr HW, et al. Carcinoma of the oral cavity. factors affecting treatment failure at the primary site and neck. *Am J Surg* 1976; 132(4):504-507.
 228. Takagi M, Kayano T, Yamamoto H, et al. Causes of oral tongue cancer treatment failures. Analysis of autopsy cases. *Cancer* 1992; 69(5):1081-1087.
 229. Yamamoto E, Miyakawa A, Kohama G. Mode of invasion and lymph node metastasis in squamous cell carcinoma of the oral cavity. *Head Neck Surg* 1984; 6(5):938-947.
 230. Aygun C, Salazar OM, Sewchand W, et al. Carcinoma of the floor of the mouth: a 20-year experience. *Int J Radiat Oncol Biol Phys* 1984; 10(5):619-626.
 231. Dinshaw KA, Agarwal JP, Ghosh-Laskar S, et al. Radical radiotherapy in head and neck squamous cell carcinoma: an analysis of prognostic and therapeutic factors. *Clin Oncol (R Coll Radiol)* 2006; 18(5):383-389.
 232. Fayos JV. Management of squamous cell carcinoma of the floor of the mouth. *Am J Surg* 1972; 123(6):706-711.
 233. Liao CT, Wang HM, Hsieh LL, et al. Higher distant failure in young age tongue cancer patients. *Oral Oncol* 2006; 42(7):718-725.
 234. Sarkaria JN, Harari PM. Oral tongue cancer in young adults less than 40 years of age: rationale for aggressive therapy. *Head Neck* 1994; 16(2):107-111.
 235. Dennington ML, Carter DR, Meyers AD. Distant metastases in head and neck epidermoid carcinoma. *Laryngoscope* 1980; 90(2):196-201.
 236. Fein DA, Mendenhall WM, Parsons JT, et al. Carcinoma of the oral tongue: a comparison of results and complications of treatment with radiotherapy and/or surgery. *Head Neck* 1994; 16(4):358-365.
 237. Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer* 1977; 40(1):145-151.
 238. O'Brien PH, Carlson R, SteubnerEAJr., et al. Distant metastases in epidermoid cell carcinoma of the head and neck. *Cancer* 1971; 27(2):304-307.
 239. Probert JC, Thompson RW, Bagshaw MA. Patterns of spread of distant metastases in head and neck cancer. *Cancer* 1974; 33(1):127-133.
 240. Korb LJ, Spaulding CA, Constable WC. The role of definitive radiation therapy in squamous cell carcinoma of the oral tongue. *Cancer* 1991; 67(11):2733-2737.
 241. Cady B, Catlin D. Epidermoid carcinoma of the gum. A 20-year survey. *Cancer* 1969; 23(3):551-569.
 242. Craig RM Jr., Vickers VA, Correll RW. Erythroplastic lesion on the mandibular marginal gingiva. *J Am Dent Assoc* 1989; 119(4):543-544.
 243. Krutchkoff DJ, Chen JK, Eisenberg E, et al. Oral cancer: a survey of 566 cases from the University of Connecticut Oral Pathology Biopsy Service, 1975-1986. *Oral Surg Oral Med Oral Pathol* 1990; 70(2):192-198.
 244. Makridis SD, Mellado JR, Freedman AL, et al. Squamous cell carcinoma of gingiva and edentulous alveolar ridge: a clinicopathologic study. *Int J Periodontics Restorative Dent* 1998; 18(3):292-298.
 245. Mattick WL, Meehan DJ. Carcinoma of the gum. *Surgery* 1951; 29(2):249-254.
 246. Soo KC, Spiro RH, King W, et al. Squamous carcinoma of the gums. *Am J Surg* 1988; 156(4):281-285.
 247. Wilkins SA Jr., Vogler WR. Cancer of the gingiva. *Surg Gynecol Obstet* 1957; 105(2):145-152.
 248. Yoon TY, Bhattacharyya I, Katz J, et al. Squamous cell carcinoma of the gingiva presenting as localized periodontal disease. *Quintessence Int* 2007; 38(2):97-102.
 249. Heller AN, Klein A, Barocas A. Squamous cell carcinoma of the gingiva presenting as an endoperiodontic lesion. *J Periodontol* 1991; 62(9):573-575.
 250. Levi PA Jr., Kim DM, Harsfield SL, et al. Squamous cell carcinoma presenting as an endodontic-periodontic lesion. *J Periodontol* 2005; 76(10):1798-1804.
 251. Seoane J, Varela-Centelles PI, Walsh TF, et al. Gingival squamous cell carcinoma: diagnostic delay or rapid invasion? *J Periodontol* 2006; 77(7):1229-1233.
 252. Nomura T, Shibahara T, Cui NH, et al. Patterns of mandibular invasion by gingival squamous cell carcinoma. *J Oral Maxillofac Surg* 2005; 63(10):1489-1493.
 253. Sasaki T, Imai Y, Fujibayashi T. New proposal for T classification of gingival carcinomas arising in the maxilla. *Int J Oral Maxillofac Surg* 2004; 33(4):349-352.
 254. Simental Aea. Cancer of the hard palate and maxillary alveolar ridge: technique and applications. *Op Tech Otolaryngol* 2005; 16:28-35.
 255. Swearingen AG, McGraw JP, Palumbo VD. Roentgenographic pathologic correlation of carcinoma of the gingiva involving the mandible. *Am J Roentgenol Radium Ther Nucl Med* 1966; 96(1):15-18.
 256. Yokoo S, Umeda M, Komatsubara H, et al. Evaluation of T-classifications of upper gingival and hard palate carcinomas—a proposition for new criterion of T4. *Oral Oncol* 2002; 38(4):378-382.
 257. Holmstrup P, Pindborg JJ. Oral mucosal lesions in smokeless tobacco users. *CA Cancer J Clin* 1988; 38(4):230-235.

258. Landy JJ, White HJ. Buccogingival carcinoma of snuff dippers. *Am Surg* 1961; 27:442-447.
259. Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. *Cancer* 1957; 10(6):1300-1323.
260. Keller AZ, Terris M. The association of alcohol and tobacco with cancer of the mouth and pharynx. *Am J Public Health Nations Health* 1965; 55(10):1578-1585.
261. Merletti F, Boffetta P, Ciccone G, et al. Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Res* 1989; 49(17):4919-4924.
262. Anil S, Beena VT, Nair RG. Squamous cell carcinoma of the gingiva in an HIV-positive patient: a case report. *Dent Update* 1996; 23(10):424-425.
263. Otsubo H, Yokoe H, Miya T, et al. Gingival squamous cell carcinoma in a patient with chronic graft-versus-host disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84(2):171-174.
264. Tenzer JA, Sugarman HM, Britton JC. Squamous cell carcinoma of the gingiva found in a patient with AIDS. *J Am Dent Assoc* 1992; 123(12):65-67.
265. Fettig A, Pogrel MA, Silverman S Jr., et al. Proliferative verrucous leukoplakia of the gingiva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90(6):723-730.
266. Bagan JV, Jimenez Y, Sanchis JM, et al. Proliferative verrucous leukoplakia: high incidence of gingival squamous cell carcinoma. *J Oral Pathol Med* 2003; 32(7):379-382.
267. Barasch A, Gofa A, Krutchkoff DJ, et al. Squamous cell carcinoma of the gingiva. A case series analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 80(2):183-187.
268. Nathanson A, Jakobsson PA, Wersall J. Prognosis of squamous-cell carcinoma of the gums. *Acta Otolaryngol* 1973; 75(4):301-303.
269. Martin H. Cancer of the gums (gingivae). *Am J Surg* 1941; 54(3):769-806.
270. Tolman A, Jerrold L, Alarbi M. Squamous cell carcinoma of attached gingiva. *Am J Orthod Dentofacial Orthop* 2007; 132(3):378-381.
271. Bill TJ, Reddy VR, Ries KL, et al. Adolescent gingival squamous cell carcinoma: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 91(6):682-685.
272. Willen R, Nathanson A, Moberger G, et al. Squamous cell carcinoma of the gingiva. Histological classification and grading of malignancy. *Acta Otolaryngol* 1975; 79(1-2):146-154.
273. Chen JK, Katz RV, Krutchkoff DJ. Intraoral squamous cell carcinoma. Epidemiologic patterns in Connecticut from 1935 to 1985. *Cancer* 1990; 66(6):1288-1296.
274. Lipkin A, Miller RH, Woodson GE. Squamous cell carcinoma of the oral cavity, pharynx, and larynx in young adults. *Laryngoscope* 1985; 95(7 pt 1):790-793.
275. Schwartz S, Shklar G. Reaction of alveolar bone to invasion of oral carcinoma. *Oral Surg Oral Med Oral Pathol* 1967; 24(1):33-37.
276. Sui Y, Tanimoto K, Taguchi A, et al. Mucosal condition of the oral cavity and sites of origin of squamous cell carcinoma. *J Oral Maxillofac Surg* 1995; 53(2):144-147; discussion 8.
277. Torabinejad M, Rick GM. Squamous cell carcinoma of the gingiva. *J Am Dent Assoc* 1980; 100(6):870-872.
278. MacComb WS, Fletcher GH, Healey JE Jr. Intra-oral cavity. In: MacComb WS, Fletcher GH, ed. *Cancer of the Head and Neck*. Baltimore: Williams and Wilkins, 1967:89-151.
279. Waldron CA. Oral epithelial tumors. In: Gorlin RJ, Goldman HM, eds. *Thomas' Oral Pathology*. St. Louis, MO: CV Mosby, 1970:834-835.
280. Silverman S. *Oral Cancer*. Atlanta, 1990.
281. Pindborg JJ. *Oral Cancer and Precancer*. Bristol: John Wright and Son, 1980:86-93.
282. Shafer WH, Hine MK, Levy BM. *A Textbook of Oral Pathology*. 4th ed. Philadelphia: WB Saunders, 1983:124-126.
283. Fayos JV. Carcinoma of the mandible. Result of radiation therapy. *Acta Radiol Ther Phys Biol* 1973; 12(5):378-386.
284. Gilbert S, Tzadik A, Leonard G. Mandibular involvement by oral squamous cell carcinoma. *Laryngoscope* 1986; 96(1):96-101.
285. Erich JB, Kragh LV. Results of treatment of squamous-cell carcinoma arising in mandibular gingiva. *AMA Arch Surg* 1959; 79(1):100-105.
286. Marchetta FC, Sako K, Badillo J. Periosteal lymphatics of the mandible and intraoral carcinoma. *Am J Surg* 1964; 108:505-507.
287. Panagopoulos A. Bone involvement in maxillofacial cancer. *Am J Surg* 1959; 98:898-903.
288. Whitehouse GH. Radiological bone changes produced by intraoral squamous carcinomata involving the lower alveolus. *Clin Otolaryngol Allied Sci* 1976; 1(1):45-52.
289. Byers RM, Newman R, Russell N, et al. Results of treatment for squamous carcinoma of the lower gum. *Cancer* 1981; 47(9):2236-2238.
290. Gomez D, Faucher A, Picot V, et al. Outcome of squamous cell carcinoma of the gingiva: a follow-up study of 83 cases. *J Craniomaxillofac Surg* 2000; 28(6):331-335.
291. Munoz Guerra MF, Naval Gias L, Campo FR, et al. Marginal and segmental mandibulectomy in patients with oral cancer: a statistical analysis of 106 cases. *J Oral Maxillofac Surg* 2003; 61(11):1289-1296.
292. Wald RM Jr., Calcaterra TC. Lower alveolar carcinoma. Segmental v marginal resection. *Arch Otolaryngol* 1983; 109(9):578-582.
293. McGregor AD, MacDonald DG. Patterns of spread of squamous cell carcinoma within the mandible. *Head Neck* 1989; 11(5):457-461.
294. McGregor AD, MacDonald DG. Patterns of spread of squamous cell carcinoma to the ramus of the mandible. *Head Neck* 1993; 15(5):440-444.
295. Johnson NW. Orofacial neoplasms: global epidemiology, risk factors and recommendations for research. *Int Dent J* 1991; 41(6):365-375.
296. Shingaki S, Nomura T, Takada M, et al. Squamous cell carcinomas of the mandibular alveolus: analysis of prognostic factors. *Oncology* 2002; 62(1):17-24.
297. Reddy CR. Carcinoma of hard palate in India in relation to reverse smoking of chuttas. *J Natl Cancer Inst* 1974; 53(3):615-619.
298. Waldron CA, el-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* 1988; 66(3):323-333.
299. Chung CK, Rahman SM, Lim ML, et al. Squamous cell carcinoma of the hard palate. *Int J Radiat Oncol Biol Phys* 1979; 5(2):191-196.
300. Evans JF, Shah JP. Epidermoid carcinoma of the palate. *Am J Surg* 1981; 142(4):451-455.
301. Martin H. Tumors of the palate (benign and malignant). *Arch Surg* 1942; 44:599-635.
302. Ratzer ER, Schweitzer RJ, Frazell EL. Epidermoid carcinoma of the palate. *Am J Surg* 1970; 119(3):294-297.
303. Petruzzelli GJ, Myers EN. Malignant neoplasms of the hard palate and upper alveolar ridge. *Oncology (Williston Park)* 1994; 8(4):43-48 (discussion 50, 3).
304. Yoroza A, Sykes AJ, Slevin NJ. Carcinoma of the hard palate treated with radiotherapy: a retrospective review of 31 cases. *Oral Oncol* 2001; 37(6):493-497.

305. Kovalic JJ, Simpson JR. Carcinoma of the hard palate. *J Otolaryngol* 1993; 22(2):118–120.
306. Eneroth CM, Hjertman L, Moberger G. Squamous cell carcinomas of the palate. *Acta Otolaryngol* 1972; 73(5): 418–427.
307. Simental AA Jr., Johnson JT, Myers EN. Cervical metastasis from squamous cell carcinoma of the maxillary alveolus and hard palate. *Laryngoscope* 2006; 116(9):1682–1684.
308. Antoniadis K, Lazaridis N, Vahsevanos K, et al. Treatment of squamous cell carcinoma of the anterior faucial pillar-retromolar trigone. *Oral Oncol* 2003; 39(7):680–686.
309. Kowalski LP, Hashimoto I, Magrin J. End results of 114 extended “commando” operations for retromolar trigone carcinoma. *Am J Surg* 1993; 166(4):374–379.
310. Byers RM, Anderson B, Schwarz EA, et al. Treatment of squamous carcinoma of the retromolar trigone. *Am J Clin Oncol* 1984; 7(6):647–652.
311. Lo K, Fletcher GH, Byers RM, et al. Results of irradiation in the squamous cell carcinomas of the anterior faucial pillar-retromolar trigone. *Int J Radiat Oncol Biol Phys* 1987; 13(7):969–974.
312. Brennan CT, Sessions DG, Spitznagel EL Jr., et al. Surgical pathology of cancer of the oral cavity and oropharynx. *Laryngoscope* 1991; 101(11):1175–1197.
313. Fletcher GH, Lindberg RD. Squamous cell carcinomas of the tonsillar area and palatine arch. *Am J Roentgenol Radium Ther Nucl Med* 1966; 96(3):574–587.
314. Lane AP, Buckmire RA, Mukherji SK, et al. Use of computed tomography in the assessment of mandibular invasion in carcinoma of the retromolar trigone. *Otolaryngol Head Neck Surg* 2000; 122(5):673–677.
315. Crecco M, Vidiri A, Angelone ML, et al. Retromolar trigone tumors: evaluation by magnetic resonance imaging and correlation with pathological data. *Eur J Radiol* 1999; 32(3):182–188.
316. Ayad T, Gelinas M, Guertin L, et al. Retromolar trigone carcinoma treated by primary radiation therapy: an alternative to the primary surgical approach. *Arch Otolaryngol Head Neck Surg* 2005; 131(7):576–582.
317. Genden EM, Ferlito A, Shaha AR, et al. Management of cancer of the retromolar trigone. *Oral Oncol* 2003; 39(7): 633–637.
318. Glenn MG, Komisar A, Laramore GE. Cost-benefit management decisions for carcinoma of the retromolar trigone. *Head Neck* 1995; 17(5):419–424.
319. Shumrick DA, Quenelle DJ. Malignant disease of the tonsillar region, retromolar trigone, and buccal mucosa. *Otolaryngol Clin North Am* 1979; 12(1):115–124.
320. Skolnik EM, Campbell JM, Meyers RM. Carcinoma of the buccal mucosa and retromolar area. *Otolaryngol Clin North Am* 1972; 5(2):327–331.
321. Huang CJ, Chao KS, Tsai J, et al. Cancer of retromolar trigone: long-term radiation therapy outcome. *Head Neck* 2001; 23(9):758–763.
322. Mendenhall WM, Morris CG, Amdur RJ, et al. Retromolar trigone squamous cell carcinoma treated with radiotherapy alone or combined with surgery. *Cancer* 2005; 103(11): 2320–2325.
323. Canto MT, Devesa SS. Oral cavity and pharynx cancer incidence rates in the United States, 1975–1998. *Oral Oncol* 2002; 38(6):610–617.
324. Douglas WG, Rigual NR, Giese W, et al. Advanced soft palate cancer: the clinical importance of the parapharyngeal space. *Otolaryngol Head Neck Surg* 2005; 133(1):66–69.
325. Fee WE Jr., Schoepfel SL, Rubenstein R, et al. Squamous cell carcinoma of the soft palate. *Arch Otolaryngol* 1979; 105(12):710–718.
326. Horton D, Tran L, Greenberg P, et al. Primary radiation therapy in the treatment of squamous cell carcinoma of the soft palate. *Cancer* 1989; 63(12):2442–2445.
327. Leemans CR, Engelbrecht WJ, Tiwari R, et al. Carcinoma of the soft palate and anterior tonsillar pillar. *Laryngoscope* 1994; 104(12):1477–1481.
328. Sweet RM, Corio RL, Kornblut AD. Squamous carcinoma of the uvula. *South Med J* 1981; 74(6):681–683, 687.
329. Weber RS, Peters LJ, Wolf P, et al. Squamous cell carcinoma of the soft palate, uvula, and anterior faucial pillar. *Otolaryngol Head Neck Surg* 1988; 99(1):16–23.
330. Chung CK, Constable WC. Squamous cell carcinoma of the soft palate and uvula. *Int J Radiat Oncol Biol Phys* 1979; 5(6):845–850.
331. Russ JE, Applebaum EL, Sisson GA. Squamous cell carcinoma of the soft palate. *Laryngoscope* 1977; 87(7):1151–1156.
332. Cheng VS, Shetty KS, Deutsch M. Carcinomas of the anterior tonsillar pillar and the soft palate—uvula: treatment by radiation therapy. *Radiology* 1980; 134(2):497–450.
333. Tandon DA, Bahadur S, Rath GK. Carcinoma of the soft palate. *J Laryngol Otol* 1992; 106(2):130–132.
334. Morse DE, Kerr AR. Disparities in oral and pharyngeal cancer incidence, mortality and survival among black and white Americans. *J Am Dent Assoc* 2006; 137(2):203–212.
335. Garrett PG, Beale FA. Carcinoma of the oropharynx: soft palate. *J Otolaryngol* 1984; 13(3):165–168.
336. Hansen E, Panwala K, Holland J. Post-operative radiation therapy for advanced-stage oropharyngeal cancer. *J Laryngol Otol* 2002; 116(11):920–924.
337. Har-El G, Shaha A, Chaudry R, et al. Carcinoma of the uvula and midline soft palate: indication for neck treatment. *Head Neck* 1992; 14(2):99–101.
338. Olasz L, Nyarady Z, Nemeth A, et al. Failure of alkylating agents to improve induction chemotherapy of oropharyngeal squamous cell cancer. *Anticancer Res* 2004; 24(4): 2557–2561.
339. Barzan L, Barra S, Franchin G, et al. Squamous cell carcinoma of the posterior pharyngeal wall: characteristics compared with the lateral wall. *J Laryngol Otol* 1995; 109(2):120–125.
340. Chang L, Stevens KR, Moss WT, et al. Squamous cell carcinoma of the pharyngeal walls treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 1996; 35(3):477–483.
341. Civantos FG, Goodwin WJ Jr. Cancer of the Oropharynx. In: Myers EN, Suen JY, ed. *Cancer of the Head and Neck*. 3rd ed. Philadelphia: WB Saunders, 1996:361–380.
342. Cooper RA, Slevin NJ, Carrington BM, et al. Radiotherapy for carcinoma of the posterior pharyngeal wall. *Int J Oncol* 2000; 16(3):611–615.
343. Hart AA, Mak-Kregar S, Hilgers FJ, et al. The importance of correct stage grouping in oncology. Results of a nationwide study of oropharyngeal carcinoma in The Netherlands. *Cancer* 1995; 75(11):2656–2662.
344. Hull MC, Morris CG, Tannehill SP, et al. Definitive radiotherapy alone or combined with a planned neck dissection for squamous cell carcinoma of the pharyngeal wall. *Cancer* 2003; 98(10):2224–2231.
345. Jones AS, Stell PM. Squamous carcinoma of the posterior pharyngeal wall. *Clin Otolaryngol Allied Sci* 1991; 16(5): 462–465.
346. Mak-Kregar S, Keus RB, Balm AJ, et al. Carcinoma of the soft palate and the posterior oropharyngeal wall. *Clin Otolaryngol Allied Sci* 1994; 19(1):22–27.
347. Marks JE, Smith PG, Sessions DG. Pharyngeal wall cancer. A reappraisal after comparison of treatment methods. *Arch Otolaryngol* 1985; 111(2):79–85.
348. Spiro RH, Kelly J, Vega AL, et al. Squamous carcinoma of the posterior pharyngeal wall. *Am J Surg* 1990; 160(4): 420–423.

349. Teichgraber JF, McConnel FM. Treatment of posterior pharyngeal wall carcinoma. *Otolaryngol Head Neck Surg* 1986; 94(3):287-290.
350. Jesse RH, Fletcher GH. Metastases in cervical lymph nodes from oropharyngeal carcinoma. Treatment and results. *Am J Roentgenol Radium Ther Nucl Med* 1963; 90:990-996.
351. Weller SA, Goffinet DR, Goode RL, et al. Carcinoma of the oropharynx. Results of megavoltage radiation therapy in 305 patients. *AJR Am J Roentgenol* 1976; 126(2):236-247.
352. Cunningham MP, Catlin D. Cancer of the pharyngeal wall. *Cancer* 1967; 20(11):1859-1866.
353. Meoz-Mendez RT, Fletcher GH, Guillaumondegui OM, et al. Analysis of the results of irradiation in the treatment of squamous cell carcinomas of the pharyngeal walls. *Int J Radiat Oncol Biol Phys* 1978; 4(7-8):579-585.
354. Fein DA, Mendenhall WM, Parsons JT, et al. Pharyngeal wall carcinoma treated with radiotherapy: impact of treatment technique and fractionation. *Int J Radiat Oncol Biol Phys* 1993; 26(5):751-757.
355. Mendenhall WM, Parsons JT, Mancuso AA, et al. Squamous cell carcinoma of the pharyngeal wall treated with irradiation. *Radiother Oncol* 1988; 11(3):205-212.
356. Talton BM, Elkon D, Kim JA, et al. Cancer of the posterior hypopharyngeal wall. *Int J Radiat Oncol Biol Phys* 1981; 7(5):597-599.
357. Schwartz SM, Daling JR, Doody DR, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 1998; 90(21):1626-1636.
358. Hemminki K, Dong C, Frisch M. Tonsillar and other upper aerodigestive tract cancers among cervical cancer patients and their husbands. *Eur J Cancer Prev* 2000; 9(6):433-437.
359. Schantz SP, Byers RM, Goepfert H, et al. The implication of tobacco use in the young adult with head and neck cancer. *Cancer* 1988; 62(7):1374-1380.
360. Snijders PJ, Scholes AG, Hart CA, et al. Prevalence of mucosotropic human papillomaviruses in squamous-cell carcinoma of the head and neck. *Int J Cancer* 1996; 66(4):464-469.
361. Barrs DM, DeSanto LW, O'Fallon WM. Squamous cell carcinoma of the tonsil and tongue-base region. *Arch Otolaryngol* 1979; 105(8):479-485.
362. Givens CD Jr., Johns ME, Cantrell RW. Carcinoma of the tonsil. Analysis of 162 cases. *Arch Otolaryngol* 1981; 107(12):730-734.
363. Seda HJ, Snow JB Jr. Carcinoma of the tonsil. *Arch Otolaryngol* 1969; 89(5):756-761.
364. Beaty MM, Funk GF, Karnell LH, et al. Risk factors for malignancy in adult tonsils. *Head Neck* 1998; 20(5):399-403.
365. Guntinas-Lichius O, Peter Klussmann J, Dinh S, et al. Diagnostic work-up and outcome of cervical metastases from an unknown primary. *Acta Otolaryngol* 2006; 126(5):536-544.
366. Begum S, Gillison ML, Ansari-Lari MA, et al. Detection of human papillomavirus in cervical lymph nodes: a highly effective strategy for localizing site of tumor origin. *Clin Cancer Res* 2003; 9(17):6469-6475.
367. Zhang MQ, El-Mofty SK, Davila RM. Detection of human papilloma virus (HPV)—related squamous cell carcinoma cytologically and by in situ hybridization (ISH) in fine needle aspiration (FNA) biopsy of cervical metastasis: a tool for identifying the site of an occult head and neck primary. *Cancer Cytopathol* 2008; 114:118-123.
368. Barkley HT Jr., Fletcher GH, Jesse RH, et al. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. *Am J Surg* 1972; 124(4):462-467.
369. Fleming PM, Matz GJ, Powell WJ, et al. Carcinoma of the tonsil. *Surg Clin North Am* 1976; 56(1):125-136.
370. Jaulerry C, Rodriguez J, Brunin F, et al. Results of radiation therapy in carcinoma of the base of the tongue. The Curie Institute experience with about 166 cases. *Cancer* 1991; 67(6):1532-1538.
371. Kraus DH, Vastola AP, Huvos AG, et al. Surgical management of squamous cell carcinoma of the base of the tongue. *Am J Surg* 1993; 166(4):384-388.
372. Mak-Kregar S, Hilgers FJ, Baris G, et al. Carcinoma of the tonsillar region: comparison of two staging systems and analysis of prognostic factors. *Laryngoscope* 1990; 100(6):634-638.
373. Perez CA, Carmichael T, Devineni VR, et al. Carcinoma of the tonsillar fossa: a nonrandomized comparison of irradiation alone or combined with surgery: long-term results. *Head Neck* 1991; 13(4):282-290.
374. Quenelle DJ, Crissman JD, Shumrick DA. Tonsil carcinoma—treatment results. *Laryngoscope* 1979; 89(11):1842-1846.
375. Remmler D, Medina JE, Byers RM, et al. Treatment of choice for squamous carcinoma of the tonsillar fossa. *Head Neck Surg* 1985; 7(3):206-211.
376. Spiro JD, Spiro RH. Carcinoma of the tonsillar fossa. An update. *Arch Otolaryngol Head Neck Surg* 1989; 115(10):1186-1189.
377. Suarez C, Rodrigo JP, Herranz J, et al. Extended supraglottic laryngectomy for primary base of tongue carcinomas. *Clin Otolaryngol Allied Sci* 1996; 21(1):37-41.
378. Tong D, Laramore GE, Griffin TW, et al. Carcinoma of the tonsillar region: results of external irradiation. *Cancer* 1982; 49(10):2009-2014.
379. Weber PC, Myers EN, Johnson JT. Squamous cell carcinoma of the base of tongue. *Eur Arch Otorhinolaryngol* 1993; 250(2):63-68.
380. al-Abdulwahed S, Kudryk W, al-Rajhi N, et al. Carcinoma of the tonsil: prognostic factors. *J Otolaryngol* 1997; 26(5):296-299.
381. Charbonneau N, Gelinas M, del Vecchio P, et al. Primary radiotherapy for tonsillar carcinoma: a good alternative to a surgical approach. *J Otolaryngol* 2006; 35(4):227-234.
382. Foote RL, Schild SE, Thompson WM, et al. Tonsil cancer. Patterns of failure after surgery alone and surgery combined with postoperative radiation therapy. *Cancer* 1994; 73(10):2638-2647.
383. Genden EM, Ferlito A, Scully C, et al. Current management of tonsillar cancer. *Oral Oncol* 2003; 39(4):337-342.
384. Gourin CG, Johnson JT. Surgical treatment of squamous cell carcinoma of the base of tongue. *Head Neck* 2001; 23(8):653-660.
385. Jones AS, Rafferty M, Fenton JE, et al. Treatment of squamous cell carcinoma of the tongue base: irradiation, surgery, or palliation? *Ann Otol Rhinol Laryngol* 2007; 116(2):92-99.
386. Lee HJ, Zelefsky MJ, Kraus DH, et al. Long-term regional control after radiation therapy and neck dissection for base of tongue carcinoma. *Int J Radiat Oncol Biol Phys* 1997; 38(5):995-1000.
387. Machtay M, Perch S, Markiewicz D, et al. Combined surgery and postoperative radiotherapy for carcinoma of the base of radiotherapy for carcinoma of the base of tongue: analysis of treatment outcome and prognostic value of margin status. *Head Neck* 1997; 19(6):494-499.
388. Mak AC, Morrison WH, Garden AS, et al. Base-of-tongue carcinoma: treatment results using concomitant boost radiotherapy. *Int J Radiat Oncol Biol Phys* 1995; 33(2):289-296.
389. Malone JP, Stephens JA, Gacula JC, et al. Disease control, survival, and functional outcome after multimodal

- treatment for advanced-stage tongue base cancer. *Head Neck* 2004; 26(7):561-572.
390. Perez CA, Patel MM, Chao KS, et al. Carcinoma of the tonsillar fossa: prognostic factors and long-term therapy outcome. *Int J Radiat Oncol Biol Phys* 1998; 42(5):1077-1084.
391. Sessions DG, Lenox J, Spector GJ, et al. Analysis of treatment results for base of tongue cancer. *Laryngoscope* 2003; 113(7):1252-1261.
392. Whicker JH, DeSanto LW, Devine KD. Surgical treatment of squamous cell carcinoma of the base of the tongue. *Laryngoscope* 1972; 82(10):1853-1860.
393. Shumrick DA, Gluckman JL. Cancer of the oropharynx. In: Suen JY, Meyers EN, ed. *Cancer of the Head and Neck*. New York: Churchill Livingstone, 1981:342-371.
394. Sessions DG, Stallings JO, Brownson RJ, et al. Total glossectomy for advanced carcinoma of the base of the tongue. *Laryngoscope* 1973; 83(1):39-50.
395. Effron MZ, Johnson JT, Myers EN, et al. Advanced carcinoma of the tongue. Management by total glossectomy without laryngectomy. *Arch Otolaryngol* 1981; 107(11): 694-697.
396. Dasmahapatra KS, Mohit-Tabatabai MA, Rush BF Jr., et al. Cancer of the tonsil. Improved survival with combination therapy. *Cancer* 1986; 57(3):451-455.
397. Mizono GS, Diaz RF, Fu KK, et al. Carcinoma of the tonsillar region. *Laryngoscope* 1986; 96(3):240-244.
398. Sanghvi V. The new combined surgical approach for cancer involving the base of tongue-supraglottic complex. *Laryngoscope* 1994; 104(6 pt 1):725-730.
399. Schleuning AJ II, Summers GW. Carcinoma of the tongue: review of 220 cases. *Laryngoscope* 1972; 82(8):1446-1454.
400. Zeitels SM, Vaughan CW. Tongue-base-cancer resection with partial supraglottic laryngectomy. *Am J Otolaryngol* 1994; 15(3):197-203.
401. Chung TS, Stefani S. Distant metastases of carcinoma of tonsillar region: a study of 475 patients. *J Surg Oncol* 1980; 14(1):5-9.
402. Dahlgren L, Dahlstrand HM, Lindquist D, et al. Human papillomavirus is more common in base of tongue than in mobile tongue cancer and is a favorable prognostic factor in base of tongue cancer patients. *Int J Cancer* 2004; 112(6): 1015-1019.
403. Li W, Thompson CH, O'Brien CJ, et al. Human papillomavirus positivity predicts favourable outcome for squamous carcinoma of the tonsil. *Int J Cancer* 2003; 106(4): 553-558.
404. Lindel K, Beer KT, Laissue J, et al. Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. *Cancer* 2001; 92(4):805-813.
405. Mellin H, Friesland S, Lewensohn R, et al. Human papillomavirus (HPV) DNA in tonsillar cancer: clinical correlates, risk of relapse, and survival. *Int J Cancer* 2000; 89(3):300-304.
406. Ritchie JM, Smith EM, Summersgill KF, et al. Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. *Int J Cancer* 2003; 104(3):336-344.
407. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus-associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol* 2006; 24(5):736-747.
408. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189(1):12-19.
409. Morice WG, Ferreiro JA. Distinction of basaloid squamous cell carcinoma from adenoid cystic and small cell undifferentiated carcinoma by immunohistochemistry. *Hum Pathol* 1998; 29(6):609-612.
410. Hoffmann M, Lohrey C, Hunziker A, et al. Human papillomavirus type 16 E6 and E7 genotypes in head-and-neck carcinomas. *Oral Oncol* 2004; 40(5):520-524.
411. Paz IB, Cook N, Odom-Maryon T, et al. Human papillomavirus (HPV) in head and neck cancer. An association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. *Cancer* 1997; 79(3):595-604.
412. Kreimer AR, Clifford GM, Boyle P, et al. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005; 14(2):467-475.
413. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol* 2004; 31(6):744-754.
414. Dahlstrom KR, Adler-Storthz K, Etzel CJ, et al. Human papillomavirus type 16 infection and squamous cell carcinoma of the head and neck in never-smokers: a matched pair analysis. *Clin Cancer Res* 2003; 9(7):2620-2626.
415. Hansson BG, Rosenquist K, Antonsson A, et al. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005; 125(12):1337-1344.
416. Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 2003; 95(23):1772-1783.
417. Maden C, Beckmann AM, Thomas DB, et al. Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. *Am J Epidemiol* 1992; 135(10): 1093-1102.
418. Rosenquist K, Wennerberg J, Schildt EB, et al. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005; 125(12):1327-1336.
419. Smith EM, Ritchie JM, Summersgill KF, et al. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. *J Natl Cancer Inst* 2004; 96(6):449-455.
420. Smith EM, Ritchie JM, Summersgill KF, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer* 2004; 108(5):766-772.
421. El-mofty SK, Zhang MQ, Davila RM. Detection of HPV in metastatic squamous cell carcinoma in cervical lymph nodes: a tool for the identification of the site of occult head and neck primary. *Mod Pathol* 2007; 20:1016a.
422. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000; 18(19):3339-3345.
423. Davidson BJ, Spiro RH, Patel S, et al. Cervical metastases of occult origin: the impact of combined modality therapy. *Am J Surg* 1994; 168(5):395-399.
424. Nieder C, Gregoire V, Ang KK. Cervical lymph node metastases from occult squamous cell carcinoma: cut down a tree to get an apple? *Int J Radiat Oncol Biol Phys* 2001; 50(3):727-733.
425. Herbsleb M, Knudsen UB, Orntoft TF, et al. Telomerase activity, MIB-1, PCNA, HPV 16 and p53 as diagnostic markers for cervical intraepithelial neoplasia. *Apmis* 2001; 109(9):607-617.
426. Keating JT, Cviko A, Riethdorf S, et al. Ki-67, cyclin E, and p16INK4 are complimentary surrogate biomarkers for human papilloma virus-related cervical neoplasia. *Am J Surg Pathol* 2001; 25(7):884-891.
427. Klaes R, Friedrich T, Spitkovsky D, et al. Overexpression of p16(INK4A) as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. *Int J Cancer* 2001; 92(2):276-284.

428. Lu DW, El-Mofty SK, Wang HL. Expression of p16, Rb, and p53 proteins in squamous cell carcinomas of the anorectal region harboring human papillomavirus DNA. *Mod Pathol* 2003; 16(7):692-699.
429. Khleif SN, DeGregori J, Yee CL, et al. Inhibition of cyclin D-CDK4/CDK6 activity is associated with an E2F-mediated induction of cyclin kinase inhibitor activity. *Proc Natl Acad Sci U S A* 1996; 93(9):4350-4354.
430. Phelps WC, Barnes JA, Lobe DC. Molecular targets for human papillomaviruses: prospects for antiviral therapy. *Antivir Chem Chemother* 1998; 9(5):359-377.
431. Wilczynski SP, Lin BT, Xie Y, et al. Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma. *Am J Pathol* 1998; 152(1):145-156.
432. Boyer SN, Wazer DE, Band V. E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. *Cancer Res* 1996; 56(20):4620-4624.
433. Dyson N, Howley PM, Munger K, et al. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 1989; 243(4893):934-937.
434. van Houten VM, Snijders PJ, van den Brekel MW, et al. Biological evidence that human papillomaviruses are etiologically involved in a subgroup of head and neck squamous cell carcinomas. *Int J Cancer* 2001; 93(2):232-235.
435. Boyle JO, Hakim J, Koch W, et al. The incidence of p53 mutations increases with progression of head and neck cancer. *Cancer Res* 1993; 53(19):4477-4480.
436. Field JK, Zoumpourlis V, Spandidos DA, et al. p53 expression and mutations in squamous cell carcinoma of the head and neck: expression correlates with the patients' use of tobacco and alcohol. *Cancer Detect Prev* 1994; 18(3):197-208.
437. Hafkamp HC, Manni JJ, Speel EJ. Role of human papillomavirus in the development of head and neck squamous cell carcinomas. *Acta Otolaryngol* 2004; 124(4):520-526.
438. Evans AT, Guthrie W. Lymphoepithelioma-like carcinoma of the uvula and soft palate: a rare lesion in an unusual site. *Histopathology* 1991; 19(2):184-186.
439. Chow TL, Chow TK, Lui YH, et al. Lymphoepithelioma-like carcinoma of oral cavity: report of three cases and literature review. *Int J Oral Maxillofac Surg* 2002; 31(2):212-218.
440. Weiss LM, Movahed LA, Butler AE, et al. Analysis of lymphoepithelioma and lymphoepithelioma-like carcinomas for Epstein-Barr viral genomes by in situ hybridization. *Am J Surg Pathol* 1989; 13(8):625-631.
441. Kljanienco J, Micheau C, Azli N, et al. Undifferentiated carcinoma of nasopharyngeal type of tonsil. *Arch Otolaryngol Head Neck Surg* 1989; 115(6):731-734.
442. Bansberg SF, Olsen KD, Gaffey TA. Lymphoepithelioma of the oropharynx. *Otolaryngol Head Neck Surg* 1989; 100(4):303-307.
443. Nicholls JM, Pittaluga S, Chung LP, et al. The association between carcinoma of the tonsil and Epstein-Barr virus—a study using radiolabelled in situ hybridization. *Pathology* 1994; 26(2):94-98.
444. Barnes L, Eveson JW, Reichart P, et al. World Health Organization. Classification of Tumors: Pathology and Genetics Head and Neck Tumors. Lyon: IARC press, 2005.
445. Wain SL, Kier R, Vollmer RT, et al. Basaloid-squamous carcinoma of the tongue, hypopharynx, and larynx: report of 10 cases. *Hum Pathol* 1986; 17(11):1158-1166.
446. Banks ER, Frierson HF Jr., Mills SE, et al. Basaloid squamous cell carcinoma of the head and neck. A clinicopathologic and immunohistochemical study of 40 cases. *Am J Surg Pathol* 1992; 16(10):939-946.
447. Luna MA, el Naggar A, Parichatikanond P, et al. Basaloid squamous carcinoma of the upper aerodigestive tract. Clinicopathologic and DNA flow cytometric analysis. *Cancer* 1990; 66(3):537-542.
448. Kljanienco J, el-Naggar A, Ponzio-Prion A, et al. Basaloid squamous carcinoma of the head and neck. Immunohistochemical comparison with adenoid cystic carcinoma and squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* 1993; 119(8):887-890.
449. Wan SK, Chan JK, Tse KC. Basaloid-squamous carcinoma of the nasal cavity. *J Laryngol Otol* 1992; 106(4):370-371.
450. Wieneke JA, Thompson LD, Wenig BM. Basaloid squamous cell carcinoma of the sinonasal tract. *Cancer* 1999; 85(4):841-854.
451. Abiko Y, Muramatsu T, Tanaka Y, et al. Basaloid-squamous cell carcinoma of the oral mucosa: report of two cases and study of the proliferative activity. *Pathol Int* 1998; 48(6):460-466.
452. Cadier MA, Kelly SA, Parkhouse N, et al. Basaloid squamous carcinoma of the buccal cavity. *Head Neck* 1992; 14(5):387-391.
453. Campman SC, Gandour-Edwards RF, Sykes JM. Basaloid squamous carcinoma of the head and neck. Report of a case occurring in the anterior floor of the mouth. *Arch Pathol Lab Med* 1994; 118(12):1229-1232.
454. Coletta RD, Cotrim P, Almeida OP, et al. Basaloid squamous carcinoma of oral cavity: a histologic and immunohistochemical study. *Oral Oncol* 2002; 38(7):723-729.
455. Coppola D, Catalano E, Tang CK, et al. Basaloid squamous cell carcinoma of floor of mouth. *Cancer* 1993; 72(8):2299-2305.
456. Hellquist HB, Dahl F, Karlsson MG, et al. Basaloid squamous cell carcinoma of the palate. *Histopathology* 1994; 25(2):178-180.
457. Ide F, Shimoyama T, Horie N, et al. Basaloid squamous cell carcinoma of the oral mucosa: a new case and review of 45 cases in the literature. *Oral Oncol* 2002; 38(1):120-124.
458. Lovejoy HM, Matthews BL. Basaloid-squamous carcinoma of the palate. *Otolaryngol Head Neck Surg* 1992; 106(2):159-162.
459. Raslan WF, Barnes L, Krause JR, et al. Basaloid squamous cell carcinoma of the head and neck: a clinicopathologic and flow cytometric study of 10 new cases with review of the English literature. *Am J Otolaryngol* 1994; 15(3):204-211.
460. Seidman JD, Berman JJ, Yost BA, et al. Basaloid squamous carcinoma of the hypopharynx and larynx associated with second primary tumors. *Cancer* 1991; 68(7):1545-1549.
461. Khaldi L, Apostolidis T, Pappa DA, et al. Basaloid squamous carcinoma of the larynx. A potential diagnostic pitfall. *Ann Diagn Pathol* 2006; 10(5):297-300.
462. McKay MJ, Bilous AM. Basaloid-squamous carcinoma of the hypopharynx. *Cancer* 1989; 63(12):2528-2531.
463. Rodriguez Tojo MJ, Garcia Cano FJ, Infante Sanchez JC, et al. Immunoeexpression of p53, Ki-67 and E-cadherin in basaloid squamous cell carcinoma of the larynx. *Clin Transl Oncol* 2005; 7(3):110-114.
464. Bahar G, Feinmesser R, Popovtzer A, et al. Basaloid squamous carcinoma of the larynx. *Am J Otolaryngol* 2003; 24(3):204-208.
465. Winzenburg SM, Niehans GA, George E, et al. Basaloid squamous carcinoma: a clinical comparison of two histologic types with poorly differentiated squamous cell carcinoma. *Otolaryngol Head Neck Surg* 1998; 119(5):471-475.
466. Kim JY, Cho KJ, Lee SS, et al. Clinicopathologic study of basaloid squamous carcinoma of the upper aerodigestive tract. *J Korean Med Sci* 1998; 13(3):269-274.

467. Ishikawa O, Matsui Y, Aoki I, et al. Adenosquamous carcinoma of the pancreas: a clinicopathologic study and report of three cases. *Cancer* 1980; 46(5):1192–1196.
468. Barnes L, Johnson JT. Pathologic and Clinical Considerations in the Evaluation of Major Head and Neck Specimens Resected for Cancer. Part 1. New York: Appleton-Century-Croft; 1986.
469. Oikawa K, Tabuchi K, Nomura M, et al. Basaloid squamous cell carcinoma of the maxillary sinus: a report of two cases. *Auris Nasus Larynx* 2007; 34(1):119–123.
470. Shimaoka K, Tsukada Y. Squamous cell carcinomas and adenosquamous carcinomas originating from the thyroid gland. *Cancer* 1980; 46(8):1833–1842.
471. Cabanillas R, Rodrigo JP, Ferlito A, et al. Is there an epidemiological link between human papillomavirus DNA and basaloid squamous cell carcinoma of the pharynx? *Oral Oncol* 2007; 43(4):327–332.
472. Coletta RD, Cotrim P, Vargas PA, et al. Basaloid squamous carcinoma of the oral cavity: report of 2 cases and study of AgNOR, PCNA, p53, and MMP expression. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 91(5):563–569.
473. Salerno G, Di Vizio D, Staibano S, et al. Prognostic value of p27Kip1 expression in Basaloid Squamous Cell Carcinoma of the larynx. *BMC Cancer* 2006; 6:146.
474. Barnes L, Ferlito A, Altavilla G, et al. Basaloid squamous cell carcinoma of the head and neck: clinicopathological features and differential diagnosis. *Ann Otol Rhinol Laryngol* 1996; 105(1):75–82.
475. Emanuel P, Wang B, Wu M, et al. p63 Immunohistochemistry in the distinction of adenoid cystic carcinoma from basaloid squamous cell carcinoma. *Mod Pathol* 2005; 18(5):645–650.
476. Lu SY, Eng HL, Huang CC, et al. Basaloid squamous cell carcinoma of the sinonasal tract: report of two cases. *Otolaryngol Head Neck Surg* 2006; 134(5):883–885.
477. Gerughty RM, Hennigar GR, Brown FM. Adenosquamous carcinoma of the nasal, oral and laryngeal cavities. A clinicopathologic survey of ten cases. *Cancer* 1968; 22(6):1140–1155.
478. Abdelsayed RA, Sanguenza OP, Newhouse RF, et al. Adenosquamous carcinoma: a case report with immunohistochemical evaluation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85(2):173–177.
479. Keelawat S, Liu CZ, Roehm PC, et al. Adenosquamous carcinoma of the upper aerodigestive tract: a clinicopathologic study of 12 cases and review of the literature. *Am J Otolaryngol* 2002; 23(3):160–168.
480. Martinez-Madrigal F, Baden E, Casiraghi O, et al. Oral and pharyngeal adenosquamous carcinoma. A report of four cases with immunohistochemical studies. *Eur Arch Otorhinolaryngol* 1991; 248(5):255–258.
481. Siar CH, Ng KH. Adenosquamous carcinoma of the floor of the mouth and lower alveolus: a radiation-induced lesion? *Oral Surg Oral Med Oral Pathol* 1987; 63(2):216–220.
482. Thompson LDR. Squamous cell carcinoma variants of the head and neck. *Curr Diagn Pathol* 2003; 9(6):384–396.
483. Cerezo L, Alvarez M, Edwards O, et al. Adenosquamous carcinoma of the colon. *Dis Colon Rectum* 1985; 28(8):597–603.
484. Fitzgibbons PL, Kern WH. Adenosquamous carcinoma of the lung: a clinical and pathologic study of seven cases. *Hum Pathol* 1985; 16(5):463–466.
485. Howat AJ, Scott E, Mackie DB, et al. Adenosquamous carcinoma of the renal pelvis. *Am J Clin Pathol* 1983; 79(6):731–733.
486. Izumi K, Nakajima T, Maeda T, et al. Adenosquamous carcinoma of the tongue: report of a case with histochemical, immunohistochemical, and ultrastructural study and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85(2):178–184.
487. Mingazzini PL, Barsotti P, Malchiodi Albedi F. Adenosquamous carcinoma of the stomach: histological, histochemical and ultrastructural observations. *Histopathology* 1983; 7(3):433–443.
488. Saito R, Davis BK, Ollapally EP. Adenosquamous carcinoma of the prostate. *Hum Pathol* 1984; 15(1):87–89.
489. Weidner N, Foucar E. Adenosquamous carcinoma of the skin. An aggressive mucin- and gland-forming squamous carcinoma. *Arch Dermatol* 1985; 121(6):775–779.
490. Ellis GL, Auclair PL, Gnepp DR. Adenosquamous carcinoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:455–459.
491. Napier SS, Gormely JS, Newlands C, et al. Adenosquamous carcinoma. A rare neoplasm with an aggressive course. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 79(5):607–611.
492. Sanner JR. Combined adenosquamous carcinoma and ductal adenoma of the hard and soft palate: report of case. *J Oral Surg* 1979; 37(5):331–334.
493. Johnson WC, Helwig EB. Adenoid squamous cell carcinoma (adenocanthoma). A clinicopathologic study of 155 patients. *Cancer* 1966; 19(11):1639–1650.
494. Muller SA, Wilhelmj CM Jr., Harrison EG Jr., et al. Adenoid Squamous Cell Carcinoma (Adenocanthoma of Lever). Report of Seven Cases and Review. *Arch Dermatol* 1964; 89:589–597.
495. Blackburn TK, Macpherson D, Conroy B. Primary adenoid squamous cell carcinoma of the upper lip associated with a locoregional metastasis: a case report and review of the literature. *J Oral Maxillofac Surg* 1999; 57(5):612–616.
496. Caya JG, Hidayat AA, Weiner JM. A clinicopathologic study of 21 cases of adenoid squamous cell carcinoma of the eyelid and periorbital region. *Am J Ophthalmol* 1985; 99(3):291–297.
497. Jacoway JR, Nelson JF, Boyers RC. Adenoid squamous-cell carcinoma (adenocanthoma) of the oral labial mucosa. A clinicopathologic study of fifteen cases. *Oral Surg Oral Med Oral Pathol* 1971; 32(3):444–449.
498. Tomich CE, Hutton CE. Adenoid squamous cell carcinoma of the lip: report of cases. *J Oral Surg* 1972; 30(8):592–598.
499. Weitzner S. Adenoid squamous-cell carcinoma of vermilion mucosa of lower lip. *Oral Surg Oral Med Oral Pathol* 1974; 37(4):589–593.
500. Lever WF. Adenocanthoma of sweat glands: Carcinoma of sweat gland with glandular and epidermal elements. Report of 4 cases. *Arch Dermatol Syphilol* 1947; 56:157–171.
501. Jones AC, Freedman PD, Kerpel SM. Oral adenoid squamous cell carcinoma: a report of three cases and review of the literature. *J Oral Maxillofac Surg* 1993; 51(6):676–681.
502. Goldman RL, Klein HZ, Sung M. Adenoid squamous cell carcinoma of the oral cavity: report of the first case arising in the tongue. *Arch Otolaryngol* 1977; 103(8):496–498.
503. Takagi M, Sakota Y, Takayama S, et al. Adenoid squamous cell carcinoma of the oral mucosa: report of two autopsy cases. *Cancer* 1977; 40(5):2250–2255.
504. Ackerman L. Verrucous carcinoma of the oral cavity. *Surgery* 1948; 23:670–678.
505. Batsakis JG, Hybels R, Crissman JD, et al. The pathology of head and neck tumors: verrucous carcinoma, Part 15. *Head Neck Surg* 1982; 5(1):29–38.
506. Kraus FT, Perezmesa C. Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. *Cancer* 1966; 19(1):26–38.
507. McDonald JS, Crissman JD, Gluckman JL. Verrucous carcinoma of the oral cavity. *Head Neck Surg* 1982; 5(1):22–28.

508. Ferlito A, Recher G. Ackerman's tumor (verrucous carcinoma) of the larynx: a clinicopathologic study of 77 cases. *Cancer* 1980; 46(7):1617-1630.
509. Bacon MP, Chevetton EB, Slack RW, et al. Verrucous carcinoma of the maxillary antrum. *J Laryngol Otol* 1989; 103(4):415-416.
510. Daoud A, Lannigan FJ, McGlashan JA, et al. Verrucous carcinoma of the maxillary antrum. *J Laryngol Otol* 1991; 105(8):696-699.
511. Edelstein DR, Smouha E, Sacks SH, et al. Verrucous carcinoma of the temporal bone. *Ann Otol Rhinol Laryngol* 1986; 95(5 pt 1):447-453.
512. Hanna GS, Ali MH. Verrucous carcinoma of the nasal septum. *J Laryngol Otol* 1987; 101(2):184-187.
513. Proops DW, Hawke WM, van Nostrand AW, et al. Verrucous carcinoma of the ear. Case report. *Ann Otol Rhinol Laryngol* 1984; 93(4 pt 1):385-388.
514. Thomas JR, Snyderman SC, Giffin CS, et al. Verrucous carcinoma of the pyriform sinus. *Arch Otolaryngol* 1973; 97(6):488-489.
515. Woodson GE, Jurco S III, Alford BR, et al. Verrucous carcinoma of the middle ear. *Arch Otolaryngol* 1981; 107(1):63-65.
516. Bouquot JE. Oral verrucous carcinoma. Incidence in two US populations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86(3):318-324.
517. Goethals PL, Harrison EG Jr., Devine KD. Verrucous squamous carcinoma of the oral cavity. *Am J Surg* 1963; 106:845-851.
518. Nair MK, Sankaranarayanan R, Padmanabhan TK, et al. Oral verrucous carcinoma. Treatment with radiotherapy. *Cancer* 1988; 61(3):458-461.
519. Brandsma JL, Steinberg BM, Abramson AL, et al. Presence of human papillomavirus type 16 related sequences in verrucous carcinoma of the larynx. *Cancer Res* 1986; 46(4 pt 2):2185-2188.
520. Bryan RL, Bevan IS, Crocker J, et al. Detection of HPV 6 and 11 in tumours of the upper respiratory tract using the polymerase chain reaction. *Clin Otolaryngol Allied Sci* 1990; 15(2):177-180.
521. Fliss DM, Noble-Topham SE, McLachlin M, et al. Laryngeal verrucous carcinoma: a clinicopathologic study and detection of human papillomavirus using polymerase chain reaction. *Laryngoscope* 1994; 104(2):146-152.
522. Johnson TL, Plieth DA, Crissman JD, et al. HPV detection by polymerase chain reaction (PCR) in verrucous lesions of the upper aerodigestive tract. *Mod Pathol* 1991; 4(4): 461-465.
523. Shroyer KR, Greer RO, Fankhouser CA, et al. Detection of human papillomavirus DNA in oral verrucous carcinoma by polymerase chain reaction. *Mod Pathol* 1993; 6(6): 669-672.
524. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol* 1985; 60(3):285-298.
525. Murrah VA, Batsakis JG. Proliferative verrucous leukoplakia and verrucous hyperplasia. *Ann Otol Rhinol Laryngol* 1994; 103(8 pt 1):660-663.
526. Koch BB, Trask DK, Hoffman HT, et al. National survey of head and neck verrucous carcinoma: patterns of presentation, care, and outcome. *Cancer* 2001; 92(1):110-120.
527. Wu M, Putti TC, Bhuiya TA. Comparative study in the expression of p53, EGFR, TGF-alpha, and cyclin D1 in verrucous carcinoma, verrucous hyperplasia, and squamous cell carcinoma of head and neck region. *Appl Immunohistochem Mol Morphol* 2002; 10(4):351-356.
528. Angadi PV, Krishnapillai R. Cyclin D1 expression in oral squamous cell carcinoma and verrucous carcinoma: correlation with histological differentiation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(3):e30-e35.
529. Prioleau PG, Santa Cruz DJ, Meyer JS, et al. Verrucous carcinoma: a light and electron microscopic, autoradiographic, and immunofluorescence study. *Cancer* 1980; 45(11):2849-2857.
530. Ogawa A, Fukuta Y, Nakajima T, et al. Treatment results of oral verrucous carcinoma and its biological behavior. *Oral Oncol* 2004; 40(8):793-797.
531. Medina JE, Dichtel W, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathologic study of 104 cases. *Arch Otolaryngol* 1984; 110(7):437-440.
532. Shear M, Pindborg JJ. Verrucous hyperplasia of the oral mucosa. *Cancer* 1980; 46(8):1855-1862.
533. Slootweg PJ, Muller H. Verrucous hyperplasia or verrucous carcinoma. An analysis of 27 patients. *J Maxillofac Surg* 1983; 11(1):13-19.
534. Zakrzewska JM, Lopes V, Speight P, et al. Proliferative verrucous leukoplakia: a report of ten cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 82(4):396-401.
535. Vedtofte P, Holmstrup P, Hjorting-Hansen E, et al. Surgical treatment of premalignant lesions of the oral mucosa. *Int J Oral Maxillofac Surg* 1987; 16(6):656-664.
536. Poh CF, Zhang L, Lam WL, et al. A high frequency of allelic loss in oral verrucous lesions may explain malignant risk. *Lab Invest* 2001; 81(4):629-634.
537. Ferlito A, Rinaldo A, Mannara GM. Is primary radiotherapy an appropriate option for the treatment of verrucous carcinoma of the head and neck? *J Laryngol Otol* 1998; 112(2):132-139.
538. McCaffrey TV, Witte M, Ferguson MT. Verrucous carcinoma of the larynx. *Ann Otol Rhinol Laryngol* 1998; 107(5 pt 1):391-395.
539. Tharp ME II, Shidnia H. Radiotherapy in the treatment of verrucous carcinoma of the head and neck. *Laryngoscope* 1995; 105(4 pt 1):391-396.
540. Parkhill E. Tumors of the palatine tonsil. In: *Tumors of the Oral Cavity and Pharynx Atlas of Tumor Pathology*. Washington, DC: Armed Forces Institute of Pathology; 1968.
541. Shanmugaratnam K, Sobin LH, Barnes L, et al. World Health Organization. *Histologic Typing of Tumors of the Upper Respiratory Tract and Ear*. 2nd. ed. Berlin, Germany: Springer-Verlag; 1991.
542. Ishiyama A, Eversole LR, Ross DA, et al. Papillary squamous neoplasms of the head and neck. *Laryngoscope* 1994; 104(12):1446-1452.
543. Thompson LD, Wenig BM, Heffner DK, et al. Exophytic and papillary squamous cell carcinomas of the larynx: A clinicopathologic series of 104 cases. *Otolaryngol Head Neck Surg* 1999; 120(5):718-724.
544. Batsakis JG, Suarez P. Papillary squamous carcinoma: will the real one please stand up? *Adv Anat Pathol* 2000; 7(1): 2-8.
545. Ferlito A, Devaney KO, Rinaldo A, et al. Papillary squamous cell carcinoma versus verrucous squamous cell carcinoma of the head and neck. *Ann Otol Rhinol Laryngol* 1999; 108(3):318-322.
546. Suarez PA, Adler-Storthz K, Luna MA, et al. Papillary squamous cell carcinomas of the upper aerodigestive tract: a clinicopathologic and molecular study. *Head Neck* 2000; 22(4):360-368.
547. Cobo F, Garcia C, Talavera P, et al. Human papillomavirus associated with papillary squamous cell carcinoma of the oropharynx in a renal transplant recipient. *Infection* 2006; 34(3):176-180.
548. Crissman JD, Kessis T, Shah KV, et al. Squamous papillary neoplasia of the adult upper aerodigestive tract. *Hum Pathol* 1988; 19(12):1387-1396.
549. Ferrer MJ, Estelles E, Villanueva A, et al. Papillary squamous cell carcinoma of the oropharynx. *Eur Arch Otorhinolaryngol* 2003; 260(8):444-445.

550. Takeda Y, Satoh M, Nakamura S, et al. Papillary squamous cell carcinoma of the oral mucosa: immunohistochemical comparison with other carcinomas of oral mucosal origin. *J Oral Sci* 2001; 43(3):165–169.

SPINDLE CELL (SARCOMATOID) CARCINOMA

1. Cardesa A ZN. Spindle cell carcinoma. In: Barnes L, EJRPeal, ed. *World Health Organization Classification of Tumours—Pathology and Genetics, Head and Neck Tumors*. Lyons, France: IARC Press, 2005:127–128.
2. Tse GM, Tan PH, Putti TC, et al. Metaplastic carcinoma of the breast: a clinicopathological review. *J Clin Pathol* 2006; 59(10):1079–1083.
3. Papi G, Corrado S, LiVolsi VA. Primary spindle cell lesions of the thyroid gland; an overview. *Am J Clin Pathol* 2006; 125(suppl):S95–S123.
4. Nappi O, Wick MR. Sarcomatoid neoplasms of the respiratory tract. *Semin Diagn Pathol* 1993; 10(2):137–147.
5. Hansen LT, Kristensen S, Moesner J. Polypoidal carcinosarcoma of the oropharynx: a clinicopathological and immunohistochemical study. *J Laryngol Otol* 1995; 109(5):459–465.
6. Batsakis JG. “Pseudosarcoma” of the mucous membranes in the head and neck. *J Laryngol Otol* 1981; 95(3):311–316.
7. Battifora H. Spindle cell carcinoma: ultrastructural evidence of squamous origin and collagen production by the tumor cells. *Cancer* 1976; 37(5):2275–2282.
8. Lichtiger B, Mackay B, Tessmer CF. Spindle-cell variant of squamous carcinoma. A light and electron microscopic study of 13 cases. *Cancer* 1970; 26(6):1311–1320.
9. Leifer C, Miller AS, Putong PB, et al. Spindle-cell carcinoma of the oral mucosa. A light and electron microscopic study of apparent sarcomatous metastasis to cervical lymph nodes. *Cancer* 1974; 34(3):597–605.
10. Zarbo RJ, Crissman JD, Venkat H, et al. Spindle-cell carcinoma of the upper aerodigestive tract mucosa. An immunohistologic and ultrastructural study of 18 biphasic tumors and comparison with seven monophasic spindle-cell tumors. *Am J Surg Pathol* 1986; 10(11):741–753.
11. Thompson LD, Wieneke JA, Miettinen M, et al. Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. *Am J Surg Pathol* 2002; 26(2): 153–170.
12. Lewis JE, Olsen KD, Sebo TJ. Spindle cell carcinoma of the larynx: review of 26 cases including DNA content and immunohistochemistry. *Hum Pathol* 1997; 28(6):664–673.
13. Slootweg PJ, Roholl PJ, Muller H, et al. Spindle-cell carcinoma of the oral cavity and larynx. Immunohistochemical aspects. *J Craniomaxillofac Surg* 1989; 17(5):234–236.
14. Olsen KD, Lewis JE, Suman VJ. Spindle cell carcinoma of the larynx and hypopharynx. *Otolaryngol Head Neck Surg* 1997; 116(1):47–52.
15. Lewis JS, Ritter JH, El-Mofty S. Alternative epithelial markers in sarcomatoid carcinomas of the head and neck, lung, and bladder-p63, MOC-31, and TTF-1. *Mod Pathol* 2005; 18(11):1471–1481.
16. Ellis GL, Langloss JM, Heffner DK, et al. Spindle-cell carcinoma of the aerodigestive tract. An immunohistochemical analysis of 21 cases. *Am J Surg Pathol* 1987; 11(5): 335–342.
17. Choi HR, Sturgis EM, Rosenthal DI, et al. Sarcomatoid carcinoma of the head and neck: molecular evidence for evolution and progression from conventional squamous cell carcinomas. *Am J Surg Pathol* 2003; 27(9):1216–1220.
18. Torenbeek R, Hermen MA, Meijer GA, et al. Analysis by comparative genomic hybridization of epithelial and spindle cell components in sarcomatoid carcinoma and carcinosarcoma: histogenetic aspects. *J Pathol* 1999; 189(3):338–343.
19. Onoue T, Uchida D, Begum NM, et al. Epithelial-mesenchymal transition induced by the stromal cell-derived factor-1/CXCR4 system in oral squamous cell carcinoma cells. *Int J Oncol* 2006; 29(5):1133–1138.
20. Cano A, Perez-Moreno MA, Rodrigo I, et al. The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. *Nat Cell Biol* 2000; 2(2):76–83.
21. Ellis GL, Corio RL. Spindle cell carcinoma of the oral cavity. A clinicopathologic assessment of fifty-nine cases. *Oral Surg Oral Med Oral Pathol* 1980; 50(6):523–533.
22. Leventon GS, Evans HL. Sarcomatoid squamous cell carcinoma of the mucous membranes of the head and neck: a clinicopathologic study of 20 cases. *Cancer* 1981; 48(4):994–1003.
23. Srinivasan U, Talvalkar GV. True carcinosarcoma of the larynx: a case report. *J Laryngol Otol* 1979; 93(10):1031–1035.
24. Goldman RL, Weidner N. Pure squamous cell carcinoma of the larynx with cervical nodal metastasis showing rhabdomyosarcomatous differentiation. Clinical, pathologic, and immunohistochemical study of a unique example of divergent differentiation. *Am J Surg Pathol* 1993; 17(4):415–421.
25. Banerjee SS, Eyden BP, Wells S, et al. Pseudoangiosarcomatous carcinoma: a clinicopathological study of seven cases. *Histopathology* 1992; 21(1):13–23.
26. Pitt MA, Morphopoulos G, Wells S, et al. Pseudoangiosarcomatous carcinoma of the genitourinary tract. *J Clin Pathol* 1995; 48(11):1059–1061.
27. Zidar N, Gale N, Zuperc A, et al. Pseudovascular adenoid squamous-cell carcinoma of the oral cavity—a report of two cases. *J Clin Pathol* 2006; 59(11):1206–1208.
28. Takata T, Ito H, Ogawa I, et al. Spindle cell squamous carcinoma of the oral region. An immunohistochemical and ultrastructural study on the histogenesis and differential diagnosis with a clinicopathological analysis of six cases. *Virchows Arch A Pathol Anat Histopathol* 1991; 419(3):177–182.
29. Weidner N. Sarcomatoid carcinoma of the upper aerodigestive tract. *Semin Diagn Pathol* 1987; 4(2):157–168.
30. Favia G, Lo ML, Serpico R, et al. Angiosarcoma of the head and neck with intra-oral presentation. A clinico-pathological study of four cases. *Oral Oncol* 2002; 38(8):757–762.
31. Gray MH, Rosenberg AE, Dickersin GR, et al. Cytokeratin expression in epithelioid vascular neoplasms. *Hum Pathol* 1990; 21(2):212–217.
32. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. *Am J Surg Pathol* 1998; 22(6): 683–697.
33. Meer S, Coleman H, Altini M. Oral synovial sarcoma: a report of 2 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(3): 306–315.
34. Benninger MS, Kraus D, Sebek B, et al. Head and neck spindle cell carcinoma: an evaluation of current management. *Cleve Clin J Med* 1992; 59(5):479–482.
35. Su HH, Chu ST, Hou YY, et al. Spindle cell carcinoma of the oral cavity and oropharynx: factors affecting outcome. *J Chin Med Assoc* 2006; 69(10):478–483.

NEUROENDOCRINE CARCINOMA

1. Chan JK, Suster S, Wenig BM, et al. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites. *Am J Surg Pathol* 1997; 21:226–234.

2. Soussi AC, Benghiat A, Holgate CS, et al. Neuroendocrine tumors of the head and neck. *J Laryngol Otol* 1990; 104:504–507.
3. Yom SS, Rosenthal DI, El-Naggar AK, et al. Merkel cell carcinoma of the tongue and head and neck mucosal sites. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 101:761–768.
4. Kim S, Jang H. Small cell carcinoma of the oral cavity: report of a case. *J Oral Maxillofac Surg* 2001; 59:680–684.
5. Baker P, Alguacil-Garcia A. Moderately differentiated neuroendocrine carcinoma in the floor of the mouth: a case report. *J Oral Maxillofac Surg* 1999; 57:1143–1147.
6. Benning TL, Vollmer RT, Crain BJ, et al. Neuroendocrine carcinoma of the oral cavity. *Mod Pathol* 1990; 3(5): 631–634.
7. Nagy J, Feher LZ, Sonkodi I, et al. A second field meta-chronous Merkel cell carcinoma of the lip and the palatine tonsil confirmed by microarray-based comparative genomic hybridization. *Virchows Arch* 2005; 446:278–286. [Epub 2005, Feb 25].
8. Barker JL, Glisson BS, Garden AS, et al. Management of nonsinonasal neuroendocrine carcinomas of the head and neck. *Cancer* 2003; 98(11):2322–2328.
9. Brambilla E, Lantuejoul S, Pugatch B, et al. Large cell carcinoma. In: Travis W, Brambilla E, Muller-Hermelink HK, et al. eds. *World Health Organization Classification of Tumours—Pathology and Genetics, Tumours of the Lung, Pleura, Thymus, and Heart*. Lyon, France: IARC Press, 2004:45–50.
10. Barnes L, Slootweg P, Tse LLY, et al. Tumours of the hypopharynx, larynx, and trachea. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours—Pathology and Genetics, Head and Neck Tumors*. Lyon, France: IARC Press, 2005:107–162.
11. Agoff SN, Lamps LW, Philip AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. *Mod Pathol* 2000; 13(3):238–242.
12. Longo F. NE carcinoma (Merkel) of oral mucosa. *J Oral Pathol Med* 1999; 28(2):88–91.
13. Inoue T, Shimono M, Takano N, et al. Merkel cell carcinoma of palatal mucosa in a young adult: immunohistochemical and ultrastructural features. *Oral Oncol* 1997; 33:226–229.
14. Vigneswaran N, Müller S, Lense E, et al. Merkel cell carcinoma of the labial mucosa. An immunohistochemical and ultrastructural study with a review of the literature on oral Merkel cell carcinoma. *Oral Surg Oral Med Oral Pathol* 1992; 74:193–200.
15. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol* 2002; 15(3):264–278.
16. Morice WG, Ferreiro JA. Distinction of basaloid squamous cell carcinoma from adenoid cystic and small cell undifferentiated carcinoma by immunohistochemistry. *Hum Pathol* 1998; 29(6):609–612.
17. Serrano MF, El-Mofty SK, Gnepp DR, et al. Utility of high molecular weight cytokeratins, but not p63, in the differential diagnosis of neuroendocrine and basaloid carcinoma of the head and neck. *Hum Pathol* 2008; 39(4):591–598. [Epub 2008, Mar 4].
18. Kim RY, Perry SR, Levy DS. Metastatic carcinoma to the tongue – a report of two cases and a review of the literature. *Cancer* 1979; 43:386–389.
19. Piatelli A, Tamborrino F. Soft palate metastasis from a small cell carcinoma of the lung. *Acta Stomatol Belg* 1995; 92(1):31–33.

ORAL MUCOSAL MALIGNANT MELANOMA

1. Hicks MJ, Flaitz CM. Oral mucosal melanoma: epidemiology and pathobiology. *Oral Oncol* 2000; 36(2):152–169.
2. Quevedo WC Jr., Fleischmann RD. Developmental biology of mammalian melanocytes. *J Invest Dermatol* 1980; 75(1): 116–120.
3. Hatch CL. Pigmented lesions of the oral cavity. *Dent Clin North Am* 2005; 49(1):185–201, ix–x.
4. Eisen D, Voorhees JJ. Oral melanoma and other pigmented lesions of the oral cavity. *J Am Acad Dermatol* 1991; 24(4):527–537.
5. Buchner A, Merrell PW, Carpenter WM. Relative frequency of solitary melanocytic lesions of the oral mucosa. *J Oral Pathol Med* 2004; 33(9):550–557.
6. Buchner A, Hansen LS. Pigmented nevi of the oral mucosa: a clinicopathologic study of 36 new cases and review of 155 cases from the literature. Part I: A clinicopathologic study of 36 new cases. *Oral Surg Oral Med Oral Pathol* 1987; 63(5):566–572.
7. Buchner A, Hansen LS. Melanotic macule of the oral mucosa. A clinicopathologic study of 105 cases. *Oral Surg Oral Med Oral Pathol* 1979; 48(3):244–249.
8. Goode RK, Crawford BE, Callihan MD, et al. Oral melanoacanthoma. Review of the literature and report of ten cases. *Oral Surg Oral Med Oral Pathol* 1983; 56(6): 622–628.
9. Chiu NT, Weinstock MA. Melanoma of oronasal mucosa. Population-based analysis of occurrence and mortality. *Arch Otolaryngol Head Neck Surg* 1996; 122(9):985–988.
10. Ostman J, Anneroth G, Gustafsson H, et al. Malignant oral tumours in Sweden 1960–1989—an epidemiological study. *Eur J Cancer B Oral Oncol* 1995; 31B(2):106–112.
11. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. *J Am Acad Dermatol* 2007; 56(5):828–834.
12. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007; 57(1):43–66.
13. Smyth AG, Ward-Booth RP, Avery BS, et al. Malignant melanoma of the oral cavity—an increasing clinical diagnosis? *Br J Oral Maxillofac Surg* 1993; 31(4):230–235.
14. Kahn MA, Weathers DR, Hoffman JG. Transformation of a benign oral pigmentation to primary oral melanoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 100(4):454–459.
15. Umeda M, Komatsubara H, Shibuya Y, et al. Premalignant melanocytic dysplasia and malignant melanoma of the oral mucosa. *Oral Oncol* 2002; 38(7):714–722.
16. Buchner A, Hansen LS. Pigmented nevi of the oral mucosa: a clinicopathologic study of 32 new cases and review of 75 cases from the literature. Part II. Analysis of 107 cases. *Oral Surg Oral Med Oral Pathol* 1980; 49(1):55–62.
17. Rapini RP, Golitz LE, Greer RO Jr., et al. Primary malignant melanoma of the oral cavity. A review of 177 cases. *Cancer* 1985; 55(7):1543–1551.
18. Loree TR, Mullins AP, Spellman J, et al. Head and neck mucosal melanoma: a 32-year review. *Ear Nose Throat J* 1999; 78(5):372–375.
19. Barker BF, Carpenter WM, Daniels TE, et al. Oral mucosal melanomas: the WESTOP Banff workshop proceedings. Western Society of Teachers of Oral Pathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 83(6): 672–679.
20. Chaudhry AP, Hampel A, Gorlin RJ. Primary malignant melanoma of the oral cavity: a review of 105 cases. *Cancer* 1958; 11(5):923–928.
21. Gu GM, Epstein JB, Morton TH Jr. Intraoral melanoma: long-term follow-up and implication for dental clinicians.

- A case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(4):404–413.
22. Rapini RP. Oral melanoma: diagnosis and treatment. *Semin Cutan Med Surg* 1997; 16(4):320–322.
 23. Pandey M, Abraham EK, Mathew A, et al. Primary malignant melanoma of the upper aero-digestive tract. *Int J Oral Maxillofac Surg* 1999; 28(1):45–49.
 24. van der Waal RI, Snow GB, Karim AB, et al. Primary malignant melanoma of the oral cavity: a review of eight cases. *Br Dent J* 1994; 176(5):185–188.
 25. Prasad ML, Jungbluth AA, Iversen K, et al. Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. *Am J Surg Pathol* 2001; 25(6):782–787.
 26. Prasad ML, Patel SG, Busam KJ. Primary mucosal desmoplastic melanoma of the head and neck. *Head Neck* 2004; 26(4):373–377.
 27. Ueta E, Miki T, Osaki T, et al. Desmoplastic malignant melanoma of the gingiva: case report and review of the literature. *Eur J Cancer B Oral Oncol* 1996; 32B(6):423–427.
 28. Batsakis JG, Bauer R, Regezi JA, et al. Desmoplastic melanoma of the maxillary alveolus. *J Oral Surg* 1979; 37(2):107–109.
 29. Kilpatrick SE, White WL, Browne JD. Desmoplastic malignant melanoma of the oral mucosa. An underrecognized diagnostic pitfall. *Cancer* 1996; 78(3):383–389.
 30. Carlson JA, Dickersin GR, Sober AJ, et al. Desmoplastic neurotropic melanoma. A clinicopathologic analysis of 28 cases. *Cancer* 1995; 75(2):478–494.
 31. Umeda M, Shimada K. Primary malignant melanoma of the oral cavity—its histological classification and treatment. *Br J Oral Maxillofac Surg* 1994; 32(1):39–47.
 32. Takagi M, Ishikawa G, Mori W. Primary malignant melanoma of the oral cavity in Japan. With special reference to mucosal melanosis. *Cancer* 1974; 34(2):358–370.
 33. Regezi JA, Hayward JR, Pickens TN. Superficial melanomas of oral mucous membranes. *Oral Surg Oral Med Oral Pathol* 1978; 45(5):730–740.
 34. Coleman WP III, Loria PR, Reed RJ, et al. Acral lentiginous melanoma. *Arch Dermatol* 1980; 116(7):773–776.
 35. Sutherland CM, Mather FJ, Muchmore JH, et al. Acral lentiginous melanoma. *Am J Surg* 1993; 166(1):64–67.
 36. Batsakis JG, Suarez P, El-Naggar AK. Mucosal melanomas of the head and neck. *Ann Otol Rhinol Laryngol* 1998; 107(7):626–630.
 37. Barrett AW, Bennett JH, Speight PM. A clinicopathological and immunohistochemical analysis of primary oral mucosal melanoma. *Eur J Cancer B Oral Oncol* 1995; 31B(2):100–105.
 38. Billings KR, Wang MB, Sercarz JA, et al. Clinical and pathologic distinction between primary and metastatic mucosal melanoma of the head and neck. *Otolaryngol Head Neck Surg* 1995; 112(6):700–706.
 39. Eneroth CM. Malignant melanoma of the oral cavity. *Int J Oral Surg* 1975; 4(5):191–197.
 40. Eneroth CM, Lundberg C. Mucosal malignant melanomas of the head and neck with special reference to cases having a prolonged clinical course. *Acta Otolaryngol* 1975; 80(5–6):452–458.
 41. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 1998; 83(8):1664–1678.
 42. Stern SJ, Guillaumondegui OM. Mucosal melanoma of the head and neck. *Head Neck* 1991; 13(1):22–27.

Diseases of the Nasal Cavity, Paranasal Sinuses, and Nasopharynx

Leon Barnes

Department of Pathology, University of Pittsburgh Medical Center, Presbyterian-University Hospital, Pittsburgh, Pennsylvania, U.S.A.

I. RHINOSINUSITIS (RHINITIS, SINUSITIS)

A. Introduction

Inflammation of the sinonasal tract may be limited to the nasal cavity (rhinitis) or to the paranasal sinuses (sinusitis) or, as in most cases, involve both sites (rhinosinusitis). It may also be unilateral or bilateral and acute, subacute, chronic, or granulomatous, with or without polyps and radiographic air-fluid levels.

Rhinosinusitis affects all age groups and is one of the most common health problems in the United States, with an annual expenditure of millions of dollars for over-the-counter medications. Signs and symptoms vary in severity and usually include one or more of those listed in Table 1. A classification of adult rhinosinusitis based on severity and duration of disease has been proposed by a Task Force of the American Academy of Otolaryngology—Head and Neck Surgery (Tables 1 and 2) (1).

There are many causes of rhinosinusitis that are not always apparent, either clinically or on histological evaluation (Table 3). Regardless of etiology, the ostiomeatal complex plays a fundamental role in the pathogenesis of most, if not all, cases of rhinosinusitis. The ostiomeatal complex is a functional unit that consists of the maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris, and middle turbinate. The key element is the maintenance of optimal sinus ventilation and drainage. Ostial obstruction creates an increasingly hypoxic environment within the sinus and a microbiological flora that becomes more anaerobic. Secretions stagnate, ciliary and epithelial damage become more severe, and inflammation and bacterial infection supervene (2). Only by ensuring ostial patency, aeration, and drainage can the cycle be broken.

B. Pathology

With few exceptions, the pathology of rhinosinusitis is rather nonspecific (Fig. 1). The lamina propria, depending on the stage of disease, may be either edematous or fibrotic and typically contains a diffuse infiltrate of lymphocytes, histiocytes, and eosinophils

with a small admixed component of neutrophils. The overlying ciliated respiratory mucosa may show focal squamous metaplasia and/or ulceration or exhibit mild papillary hyperplasia. Goblet cells, both in the mucosa and mucoserous glands, are often increased, and the basement membrane may be prominent, thick, and hyalinized. Occasionally, the glands are dilated or cystic and filled with mucus. Lymphoid aggregates are uncommon.

Unexpected findings might include large numbers of neutrophils, granulomas, or vasculitis, which should then raise the possibilities of an infectious origin or a systemic disease such as sarcoid and Wegener's granulomatosis.

C. Complications

Considering its frequency, rhinosinusitis is a relatively innocuous disorder with few complications. Nevertheless, when the inflammatory process extends into adjacent structures, treatment can be challenging and the end results sometimes deadly (3–5).

Complications of rhinosinusitis can be divided into osseous, orbital, and intracranial. Osseous involvement is most often associated with frontal sinusitis but can involve any site. The inflammation may cause bone remodeling in the form of proliferation (osteoblastic osteitis) or lysis or result in osteomyelitis (Fig. 2). Orbital or periorbital manifestations include cellulitis and abscess. Intracranial involvement is the most feared and potentially life threatening and ranges from meningitis, subdural-epidural-intracranial abscesses, and cerebritis to cavernous or superior sagittal sinus thrombosis.

Allergic Rhinosinusitis

Allergic rhinosinusitis is the most common form of atopic disease and affects 10% to 20% of the adult population in the United States (6). The incidence is higher, about 30%, among those who have a parent with a history of atopic disease, and even more so, if both parents have such a history (7). Approximately 20% to 40% of patients with allergic rhinosinusitis also have coexistent asthma (8,9).

Table 1 Signs and Symptoms of Rhinosinusitis

Major factors	Minor factors
Facial pain/pressure	Headache
Facial congestion/fullness	Fever (nonacute)
Nasal obstruction/blockage	Halitosis
Nasal discharge/purulence/ discolored postnasal drainage	Fatigue
Hyposmia/anosmia	Dental pain
Purulence in nasal cavity on Examination	Cough
Fever (acute rhinosinusitis only)	Ear pain/pressure/fullness

Source: From Ref. 1.

Table 2 Classification of Adult Rhinosinusitis

Classification	Duration	Criteria
Acute	≤ 4 wk	≥ 2 major factors, 1 major factor and 2 minor factors, or nasal purulence on examination (see Table 1) ^a
Subacute	4–12 wk	Same as chronic
Recurrent acute	≥ 4 episodes per yr, with each lasting ≥ 7–10 days and absence of intervening signs and symptoms of chronic rhinosinusitis	Same as acute
Chronic	≥ 12 wk	≥ 2 major factors, 1 major factor, and 2 minor factors or nasal purulence on examination
Acute exacerbations of chronic	Sudden worsening of chronic rhinosinusitis, with return to baseline after treatment	

^aSee Table 1 for definition of major and minor factors.

Source: From Ref. 1.

The disease is mediated through a type I IgE immunological reaction. The nose acts as a filter, effectively preventing particles of 5 to 10 μm or more in diameter from reaching the lungs (10). The particles are in contact with the nasal mucosa for about 10 to 30 minutes before they are eliminated through the pharynx by ciliary action (11). During transit some are digested by lysozyme, releasing potential allergens. In a sensitized individual, IgE antibodies attached to the surface of mast cells and basophils in the nasal mucosa react with the allergens, releasing various pharmacological mediators (histamine, prostaglandins, leukotrienes, and such) responsible for vasodilation, increased vascular permeability, edema, smooth muscle contraction, eosinophilia, nasal congestion, rhinorrhea, sneezing, and itching (12). The reaction begins within two to five minutes of antigen-antibody exposure, reaching its peak about 15 minutes later (13). This is followed four to six hours later by a second phase of mediator release from additional cells (neutrophils and eosinophils).

Table 3 Classification of Rhinosinusitis

1. Allergic
2. Infectious
 - A. Bacterial
 - B. Viral
 - C. Fungal
 - D. Mycobacterial
 - E. Others
3. Vasomotor
4. Atrophic
5. Aspirin intolerance—Samter's triad
6. NARES syndrome
7. Rhinosinusitis medicamentosa
8. Rhinosinusitis of pregnancy
 - A. Other hormonal
9. Occupational or environmental
10. Structural or mechanical
 - A. Immotile cilia (primary ciliary dyskinesia)
 - B. Septal deviation
 - C. Tumors
11. Factitial
 - A. Foreign bodies
 - B. "Nose-pickers"
12. Systemic diseases
 - A. Asthma
 - B. Cystic fibrosis
 - C. Kartagener's syndrome
 - D. Young's syndrome
 - E. Diabetes mellitus
 - F. Yellow nail syndrome
 - G. Others
13. Idiopathic

Abbreviation: NARES, nonallergic rhinosinusitis with eosinophilia.

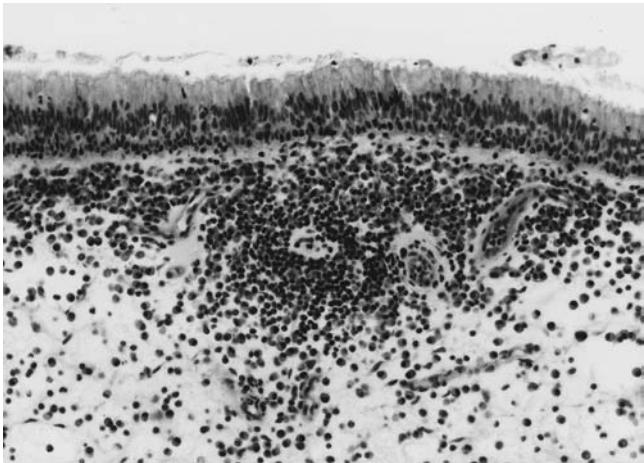


Figure 1 Chronic nonspecific rhinosinusitis. The ciliated respiratory epithelium is intact and rests upon a thin, delicate basement membrane. The lamina propria is edematous and contains a marked infiltrate of chronic inflammatory cells. There is no thickening or hyalinization of the basement membrane, no significant accumulation of eosinophils or neutrophils, and no evidence of organisms, granulomas, vasculitis, or tumor (H&E, 200×).

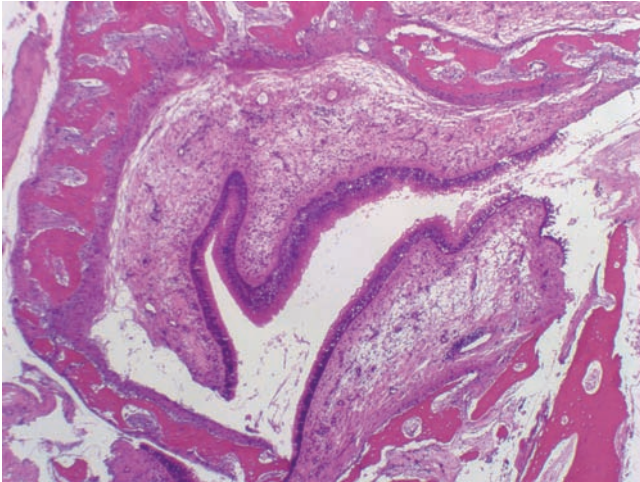


Figure 2 Chronic rhinosinusitis associated with a peripheral bony shell of reactive osteitis (H&E, 100×).

The most common allergens are pollens of grasses, weeds, and trees; animal danders; dust mites; mold spores; and food. The hallmark of the disease is the temporal correlation of nasal symptoms with exposure to an allergen. On rhinoscopy, the allergic nasal mucosa appears pale, with clear or, if infected, purulent rhinorrhea. In addition to history, the diagnosis is further supported by finding eosinophils in stained smears of nasal secretions. If more than 25% of the cells on the slide are eosinophils, allergy is very likely and, especially so, if the total serum IgE level is also evaluated.

Patients who have allergic rhinosinusitis may, on occasions, have negative skin tests when challenged with the offending allergen. The explanation for this paradox is that IgE antibodies can be synthesized locally in the nasal mucosa (14,15). The local tissue would be more sensitive to a heavy concentration of antibody than a distant skin site, resulting in rhinosinusitis and negative skin tests, respectively. Local synthesis of IgE could also explain why some patients with low serum IgE levels still have atopic symptoms.

Infectious Rhinosinusitis

A variety of infectious agents may involve the sinonasal mucosa, resulting in acute or chronic inflammation, with or without secondary polyp formation. The presence of large numbers of tissue neutrophils should always suggest the possibility of a bacterial infection.

The “common cold” is the most frequent infectious malady of the upper respiratory tract. The clinical manifestations of this viral infection are primarily a watery and profuse nasal discharge that usually persists for less than one week. The most commonly implicated viruses are rhinoviruses, parainfluenza and influenza viruses, adenoviruses, and respiratory syncytial virus (16). The typical cold remains primarily a viral rhinitis with little significant sinusitis.

Acute bacterial rhinosinusitis most commonly develops as a complication of a viral infection of the upper respiratory tract. Approximately 0.5% to 2.0% of cases of viral rhinosinusitis develop into bacterial infections (17). If a mucopurulent discharge develops, then a secondary bacterial superinfection has most likely occurred as a result of swollen nasal mucosa obstructing a sinus ostium. Decreasing sinus aeration causes decreasing oxygen tension within the sinus, and an alteration of the normal bacterial flora, ending in an acute bacterial sinusitis. Clinically, bacterial sinusitis is usually associated with the pain localized over the affected sinus.

The most common pathogens are *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, and α -hemolytic streptococci. Rarely, *Staphylococcus aureus* and *Pseudomonas* infections can occur (17). Pathogenic anaerobes are a rare cause of acute sinusitis. However, anaerobes predominate in cases of chronic sinusitis with persistent low intrasinus oxygen tension. These include peptostreptococci, *Bacteroids* sp., and fusobacteria (18,19). In the case of the maxillary sinus, it is estimated that 10% to 20% of the infections are secondary to dental infection or complication of a tooth extraction (19). Bacterial sinusitis often resolves within four to seven days of antibiotic therapy.

As acute bacterial sinusitis results from sinus ostial obstruction, it is in effect a sinus-by-sinus event, rather than a generalized process. Thus, it is more common to find contiguous unilateral sinusitis, rather than pansinusitis. Even when both maxillary antra are affected, one is usually more severely afflicted than the other. Generally, asymmetrical sinusitis is a hallmark of bacterial disease. By comparison, pansinusitis is usually found in patients with an allergic sinusitis, because the allergic process is typically a systemic, rather than local, event.

Chronic sinusitis results from either persistent acute inflammation or repeated bouts of acute or subacute sinusitis. Up to one-third of patients with acute sinusitis may develop chronic sinusitis. Chronic disease can result in an atrophic, sclerosing, or hypertrophic polypoid mucosa. These varied mucosal changes most often coexist with one another and with areas of acute inflammation of either an infectious or allergic etiology. Because chronically inflamed and scarred mucosa loses some of its ciliary function, it becomes vulnerable to future infection, initiating a vicious cycle of infection and reinfection. The bony sinus walls around a chronically infected sinus usually become thickened and sclerotic with reactive new bone formation (Fig. 2). Reactive bone is found with all chronic sinus inflammation, regardless of etiology, and presumably, is a response to periosteal involvement by inflammation. Nasal polyposis is an uncommon sequel to routine bacterial sinusitis.

Vasomotor Rhinosinusitis

Vasomotor rhinosinusitis is a chronic nonallergic, noninfectious form of rhinosinusitis caused by an imbalance of the autonomic nervous system that

governs the sinonasal mucosa (10,20,21). The imbalance results in overactive parasympathetic stimulation, with subsequent vasodilation, edema, hypersecretion, nasal obstruction, sneezing, and headaches localized over the bridge of the nose or frontal sinus area. Pruritus, in contrast to allergic rhinosinusitis, is not common. Some patients may have histories of additional autonomic dysfunctional states, such as the irritable bowel syndrome (22).

Many factors can exacerbate the symptoms. Among these are included cigarette smoke, strong perfumes or other odors, extremes of temperature, stress, anxiety, and fatigue.

Tissue removed from the sinonasal tract in patients with vasomotor rhinosinusitis typically shows only chronic nonspecific inflammation, with or without retention cysts. Eosinophils and mast cells are not increased, and neutrophils are sparse to absent, unless there has been superimposed infection (23).

Patients respond to different treatments. Some may benefit from anticholinergic drugs administered either orally, topically, or both, or to local application of silver nitrate (24). Others may require partial removal of the turbinates, particularly the inferior. This may be achieved either by surgery, electrocautery, cryosurgery, or laser (21). For those with severe intractable symptoms, interruption of the parasympathetic and sympathetic supply by a vidian nerve section may be required (25).

Atrophic Rhinosinusitis

Atrophic rhinosinusitis (ARS) is a chronic disease of unknown etiology characterized by a triad of findings: (i) atrophy of the nasal mucosa, (ii) crust formation, and (iii) the emission of a foul nasal odor, sometimes referred to as ozena (stench) (26,27). It occurs worldwide, but is especially common in subtropical and temperate climates, such as Southeast Asia, Africa, Egypt, India, China, Brazil, and the Mediterranean (26–29). Racial influence may also be a factor in that Asians, Latinos, and black Americans are more susceptible than natives of equatorial Africa. The disease is also more common among the poor who live in unsanitary conditions.

Rather than a single cause, multiple factors may be involved in the etiopathogenesis of ARS. Among the possibilities that have been proposed include (i) chronic bacterial infection of the sinonasal tract, (ii) nutritional deficiencies, especially iron and vitamin A, (iii) hypoenestrogenemia, (iv) autonomic instability with prolonged sympathetic stimulation and vasoconstriction, (v) an autoimmune disease, (vi) chronic exposure to irritants, (vii) end stage of a variety of chronic sinonasal infections, (viii) prior radiation exposure, and (ix) previous surgery (27,28).

Although *Klebsiella ozaenae*, nontoxic *Corynebacterium diphtheriae*, and the Perez–Hofer bacillus are often cultured from the sinonasal tract, it is uncertain whether these organisms are responsible for the disease or are just secondary invaders.

According to Shehata (27), the disease begins in childhood, especially in girls at the onset of puberty,

and manifests with nasal obstruction, epistaxis, headaches, nasal crusting, anosmia, halitosis, and the emission of the characteristic foul-smelling nasal odor (ozena) that is detectable by others at conversational distances. The disease is nonfatal, but very distressful. The patients often become social cripples and may even commit suicide.

Nasal biopsies of patients with ARS show chronic nonspecific inflammation and edema with progressive fibrosis, loss of cilia and goblet cells, squamous metaplasia, and atrophy of the mucoserous glands and turbinates. The blood vessels may be dilated, or they may show signs of endarteritis (28). Whether the latter is the cause or the result of ARS is open to speculation. The end result of the atrophic process is that nasal passages are widened and more air is inspired, which, with its drying effect, results in a vicious cycle of more crusts being formed.

There is no known cure for ARS. A variety of medical and surgical procedures, however, may offer some limited palliative effect. Among these are included antibiotics, lubricating nasal drops, nasal-cleansing procedures, correction of presumed deficiencies (iron, vitamin A, estrogen), surgical operation to narrow the air passages, and various techniques to disrupt the autonomic nerve supply of the nasal mucosa (nerve blocks, neurectomies) (29,30).

Shehata indicates that after the age of 40 years there is a tendency for some patients to show spontaneous arrest of the active disease in which the crusts and odor disappear despite the presence of the wide nasal passages (27).

Aspirin Intolerance: Samter's Triad

Samter has called attention to the fact that patients who are intolerant to aspirin often have coexistent nasal polyps and asthma (31,32). This constellation of findings, referred to as the aspirin, acetylsalicylic acid (ASA), or Samter's triad, is relatively common, affecting 2% to 3% of all asthmatics and 20% of severe asthmatics (33,34). In three series of 445, 127, and 154 nasal polyps, the incidence of the complete triad was 2%, 19.7%, and 24%, respectively (35–37).

The syndrome typically manifests during the third or fourth decade of life and begins with upper respiratory signs of rhinitis. The asthma and aspirin intolerance usually appears within one year of each other and about 5 to 10 years after the onset of rhinitis (36,38,39). Nasal polyps, in turn, develop about 10 years after the other symptoms have started, although they can occur at any time. In most instances, the syndrome appears sporadically. Rare reports of familial occurrences, however, have been described (34,38,39).

In the typical case, the patient starts to experience bronchoconstriction and rhinorrhea within minutes to three hours after ingesting aspirin, often accompanied by nausea, vomiting, intestinal cramps, and diarrhea. In addition to aspirin, some individuals may demonstrate an intolerance to other nonsteroidal anti-inflammatory drugs such as acetaminophen, indomethacin, and ibuprofen (38).

Rather than an allergic reaction, aspirin sensitivity represents a pharmacological effect that results when the ingested drug interferes with the metabolism of arachidonic acid (34). Normally, arachidonic acid, which is released from phospholipids in cell membranes, is metabolized along two alternative pathways. One pathway is concerned with the formation of prostaglandin derivatives by cyclooxygenase, whereas the other forms leukotrienes by the action of lipoxygenase. Aspirin inhibits cyclooxygenase and thereby increases the production of more leukotrienes, which are known to stimulate production of mucus, cause vasodilation and edema, and act as chemotactic factors for inflammatory cells (34).

The polyps are typically bilateral and, on histological examination, show extensive thickening and hyalinization of the basement membrane, increased goblet cells, stromal edema, and chronic inflammatory cells, including prominent eosinophils and mast cells (34,39,40). There are no histological features that distinguish the aspirin-intolerant polyp from the aspirin-tolerant polyp. Treatment consists of avoiding aspirin and other similar medications, aspirin desensitization, palliative relief of symptoms, and possible polypectomy (41).

Nonallergic Rhinosinusitis with Eosinophilia

Nonallergic rhinosinusitis with eosinophilia syndrome, or NARES, is a perennial form of rhinosinusitis characterized by the "on again-off again" symptoms of sneezing, profuse watery rhinorrhea, pruritus, and lacrimation, in conjunction with nasal eosinophilia in excess of 20% and negative intradermal skin tests (42).

The on again-off again symptomatology is one of the hallmarks of the disease. Although patients generally do not have prolonged symptom-free periods, those with less severe disease may have symptoms almost daily for several weeks to months interspersed with long periods without symptoms. In these instances, the patient is often mistaken for having "seasonal allergy." Allergic rhinosinusitis, however, can be excluded on the basis of a family history of atopic diseases and often positive skin tests.

There is some evidence suggesting that NARES may be a precursor of Samter's triad (aspirin intolerance, asthma, and nasal polyps) (43). As a group, NARES patients respond well to topical corticosteroids, supplemented, as needed, with decongestants and antihistamines.

Rhinosinusitis Medicamentosa

Nasal obstruction caused by topical or systemic medications is referred to as rhinosinusitis medicamentosa (44-46). Most often the culprit is one of the many over-the-counter nasal sprays or drops used for their vasoconstrictive action to alleviate nasal obstruction. Regular use, however, sometimes for as little as one week, may result in the patient using more medication, thereby establishing a vicious cycle of habitual dependence. Systemic drugs that may cause similar effects include oral contraceptives, reserpine, hydralazine, thioridazine (Mellaril), and propranolol (10,45).

After a careful history, the diagnosis can usually be confirmed by intranasal examination. The nasal mucosa is typically red and boggy and will not respond to topical 4% cocaine, which normally produces vasoconstriction and shrinkage of the turbinates (45).

The management of rhinosinusitis medicamentosa, according to Mabry, involves four steps: (i) make the diagnosis, (ii) reverse the mucosal changes, (iii) withdraw the offending medication, and (iv) educate the patient (45). During drug withdrawal, the obstruction often becomes worse, and as a result, the patient may need additional medications (corticosteroids) for temporary relief. After the patient has been weaned, a search should be made for the cause of the obstruction that led to the initial use of the nasal spray.

Rhinosinusitis of Pregnancy

Rhinosinusitis occurs in 30% of pregnant women, most notably in the second and third trimesters, and usually disappears within five postpartum days (47). The changes are due to the stimulatory effect of pregnancy-associated hormones on nasal mucoserous glands and increased blood volume with nasal vascular pooling and resultant airway resistance.

Although pregnancy may specifically influence the nose, Schatz and Zeiger (47) indicate that most women with rhinosinusitis during pregnancy actually have other specific entities not unique to pregnancy, such as allergic rhinosinusitis, bacterial rhinosinusitis, and so on. Emphasis, therefore, must be placed on making the correct diagnosis so that therapy can be directed as accurately, yet minimally, as necessary to achieve the desired therapeutic outcome and not damage the fetus.

Occupational-Environmental Rhinosinusitis

Although occupational-environmental rhinosinusitis has been known for many years, it has only recently received significant attention among otolaryngologists (48-52).

The workplace may be the source of many vapors or particulate matter that may result in rhinosinusitis by means of direct irritation or an allergic reaction. The list is long, but some of the noxious agents include wood dust, formaldehyde, sulfur dioxide, flour, nickel, shoe dust, and passive cigarette smoke. Chronic exposure may not only result in chronic rhinosinusitis, with or without polyps, but may also, in some instances, lead to malignant tumors.

Structural-Mechanical Rhinosinusitis

Defects of the cilia, either structural or functional, result in impaired mucociliary clearance, stagnation of secretions, and inflammation. This topic [primary ciliary dyskinesia (PCD), immotile cilia syndrome] is discussed elsewhere in this chapter.

Other mechanical derangements, such as a deviated nasal septum or any benign or malignant tumor may predispose the individual to infections. The possibility of a tumor should always be considered in any patient who presents with unilateral rhinosinusitis.

Factitial Rhinosinusitis

Some individuals are habitual “nose-pickers,” a practice that may result in significant squamous metaplasia, focal loss of the mucociliary clearance function, mucosal ulceration, and infection. Likewise, young children and mentally challenged individuals may insert a variety of foreign bodies into their nose that, if not detected by those around them, might lead to infection.

Systemic Causes of Rhinosinusitis

There are a variety of systemic diseases that may be associated with rhinosinusitis, with or without polyps. Some of these include asthma, cystic fibrosis (CF) (discussed elsewhere in this chapter), Kartagener’s syndrome, Young’s syndrome, diabetes mellitus, yellow nail syndrome, Wegener’s granulomatosis, allergic granulomatosis, and vasculitis of Churg-Strauss (53,54).

Evidence suggesting a connection between nasal polyps and diabetes mellitus is intriguing. Smith, in his series of 40 patients with nasal polyps, observed that 42% had abnormal glucose tolerance tests and 57% had a family history of diabetes (55). He stated that two conditions are necessary for their development: (i) local irritation, such as allergy or infection and (ii) fluctuating glucose levels.

The rationale for this association is as follows. As insulin diminishes, blood glucose increases, but is unable to cross cell membranes because this is an insulin-dependent reaction. When insulin is restored, the cells are presented with an increased substrate of glucose, which, in the presence of hexokinase, is phosphorylated into glucose-6-phosphate and then metabolized into various polysaccharides (hyaluronic acid, chondroitin sulfates, and heparin) and smaller hydrophilic colloids. Because nasal tissue lacks glucose-6-phosphate, this reaction is irreversible. The excess molecules, predominantly colloids, are then deposited extracellularly in the nasal mucosa where they exert an osmotic pressure, resulting in the edematous appearance characteristic of polyps (“polysaccharide nose”). Local irritation enhances this sequence of events.

Ultrastructurally, thickening of capillary basement membranes has been observed similar to that found in the microangiopathy of diabetes (56).

Idiopathic Rhinosinusitis

As the name implies, idiopathic rhinosinusitis is inflammation of the sinonasal tract in which no known or predisposing condition can be identified.

II. NASAL POLYPS**A. Introduction**

Nasal polyps are nonneoplastic inflammatory swellings of the nasal mucosa that affect 1% to 4% of the general population (1–3). Most arise from the anterior ethmoid-middle meatus and only rarely on the nasal septum (4,5). Similar polyps can occur in the paranasal sinuses (sinus polyp, sinonasal polyp).

Nasal polyps are found in a wide variety of diseases, including CF, rhinosinusitis, asthma, aspirin hypersensitivity as well as in various other conditions listed in Table 3. Although there has been much interest in their growth, development, and molecular biology, it is still unknown why some patients with rhinosinusitis develop polyps while others do not (3,6–20). It is possible that the polyp is a common histological endpoint of a variety of diseases of diverse etiology that happen to share a common bond—an inflammatory edematous mass (polyp).

B. Clinical Features

They typically occur in individuals older than 20 years and are more common in males by a ratio of 1.5:1 to 2:1 (21,22). Occurrence in children is uncommon and, when found, should always raise the possibility of CF or an infectious etiology (23). The polyps may be single or multiple, unilateral or bilateral, and are accompanied by nasal obstruction, headaches, sneezing, and rhinorrhea, which, at times, may be purulent. Exceptionally, they may also present with epistaxis, proptosis, and visual disturbance and may even erode bone (24–26).

C. Pathology

Grossly, polyps are soft, smooth, gray-pink, myxoid to mucoid, and translucent and often exhibit a prominent surface network of capillary-size vessels (Fig. 3). Microscopically, they display varying combinations of stromal edema, congestion, thickening, or hyalinization of the epithelial basement membranes, goblet cell hyperplasia, increased production of mucus with formation of mucous cysts and contain an infiltrate of eosinophils, plasma cells, lymphocytes, and mast cells. Unless the polyp is of infectious origin or secondarily infected, neutrophils are uncommon. The surface epithelium is of the respiratory type, often with areas of squamous metaplasia (Fig. 4). With long duration, the stroma may become fibrotic (Fig. 5). Nerves are rarely seen.



Figure 3 The typical nasal polyp has an edematous-myxoid gross appearance, with delicate surface vascularity, and will transilluminate.

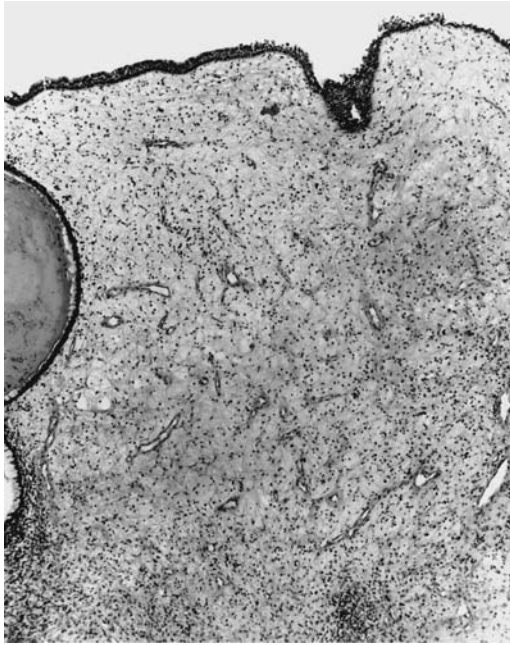


Figure 4 Nasal polyp with well-vascularized edematous stroma containing scattered inflammatory cells and a mucus-retention cyst (H&E, 50 $\times$).



Figure 5 Note the three smaller nasal polyps that are fibrotic. With long duration, polyps often become fibrotic and will not transilluminate.

Pathologists have used a variety of terms for these lesions, including allergic, simple, mucous, and inflammatory polyps. Although eosinophils and a thickened epithelial basement membrane suggest an allergic etiology, several reports have cautioned that histological features do not always correlate with the atopic status of the patient nor indicate, even at the local level, that the lesion is related to an antigen-antibody reaction (6,7,21,27,28). Therefore, the term

“allergic polyp” should not be used as a pathological diagnosis. Likewise, the term “inflammatory polyp” is potentially misleading and might be misconstrued that the polyp is of infectious origin and might result in the patient being treated unnecessarily with antibiotics. The noncommittal term “nasal polyp” is, therefore, preferred.

There is some controversy on whether all nasal polyps should be submitted for routine histological evaluation (29,30). The answer is an unequivocal “Yes!” Although clinicians are generally good at recognizing polyps, there are certainly exceptions that may be significantly more ominous than polyps and require additional investigation and therapy (30,31).

Pathologists should be aware of three important histological findings in nasal polyps: (i) stromal atypia, (ii) epithelial abnormalities, and (iii) granulomas. Atypical stromal cells are especially common in nasal polyps that have been previously biopsied or have undergone surface ulceration and necrosis. The cells are usually widely scattered throughout the stroma or around the blood vessels or just beneath the surface epithelium (Fig. 6) (32–35). These cells represent reactive histiocytes, fibroblasts, or myofibroblasts, and they typically contain enlarged, hyperchromatic, round, ovoid-to-spindled-shaped nuclei, and pink-to-amphophilic, sometimes vacuolated cytoplasm. Despite their pleomorphism, they rarely demonstrate any appreciable mitotic activity (Fig. 7). Depending on the cell of origin, they may be positive on immunostaining for α -1-antichymotrypsin, CD-68, vimentin, and actin. They are important because they are often mistaken for malignancy, especially embryonal rhabdomyosarcoma. In rhabdomyosarcoma, the tumor cells are, at least focally, densely concentrated and may even form a cambium layer; mitoses are common, cross-striations may be found, and the cells are positive for myoglobin, myogenin, or desmin. The age

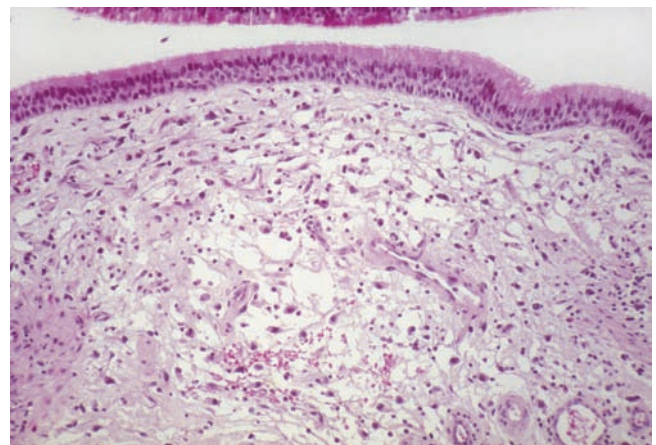


Figure 6 Nasal polyp with stromal atypia. Note that the cells with prominent, hyperchromatic nuclei are widely scattered, not densely concentrated as in some tumors (H&E, 50 $\times$).

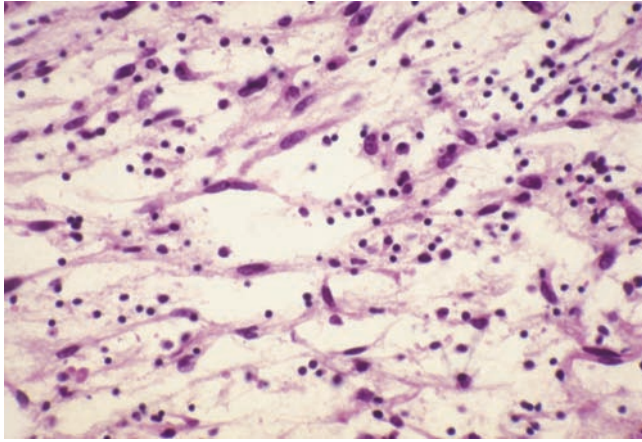


Figure 7 Higher magnification of benign, reactive stromal cells occasionally seen in nasal and antrochoanal polyps. The cells, in this instance, have elongated, hyperchromatic nuclei but show no mitotic activity. Such cells may be mistaken for strap cells of a rhabdomyosarcoma (H&E, 400 $\times$).

of the patient may also be helpful, for polyps are uncommon in individuals younger than 20 years, whereas embryonal rhabdomyosarcomas are seen more often in children.

Nakayama et al. noted in their review of 29 nasal polyps with stromal atypia that some exhibited a variable, aberrant expression for cytokeratin (CK), which might result in their being mistaken for a spindle cell squamous carcinoma (35). In spindle cell carcinoma, the tumor cells will be densely concentrated, mitotically active, and invasive. In addition, foci of dysplasia, in situ or invasive conventional squamous cell carcinoma may also be seen if the biopsy is large enough or enough sections are examined. Also in spindle cell carcinoma, the spindle cells may be positive for p63, while polyps with stromal atypia are negative.

Epithelial dysplasia or carcinoma in situ may be seen focally in 1.1% to 1.8% of all nasal polyps (36). There is no apparent correlation between the duration of the disease and the severity of these epithelial alterations. Follow-up has shown simple polypectomy to be curative. Hasegawa et al. have also reported a case of a microinvasive squamous cell carcinoma arising in a nasal polyp (37). The patient received no further treatment, other than polypectomy, and was stated to be free of disease six months later.

Westra et al. have also observed that patients receiving chemotherapy, especially alkylating agents, may exhibit epithelial atypia of the sinonasal tract (38). The distribution of the abnormal cells was distributed unevenly throughout the mucosa. In other areas, the cells occupied the full thickness of the epithelium reminiscent of high-grade dysplasia or carcinoma in situ. In addition to the clinical history that should alert the pathologist to chemotherapeutic-induced atypia, Westra et al. noticed that the abnormal cells were not associated with appreciable mitotic activity and that

the percentage of cells expressing Ki-67 was very low. Moreover, the bizarre cells were not associated with hyperplasia of the basal cell layer. Rather, the atypical cells were often found in the superficial layer of the respiratory mucosa, sparing the basal cell compartment.

Granulomas are identified in about 1% of all nasal polyps (39). Some are clearly related to intranasal corticosteroid injections, inhalation or application of medicinals with oily bases (paraffinoma), ruptured mucous cysts, or cholesterol granulomas (CGs) (40,41). Others are due to sarcoid, tuberculosis, other infectious granulomatous diseases, Wegener's granulomatosis, and so forth.

D. Treatment and Prognosis

Effective treatment consists of relieving the nasal obstruction and identifying the etiology. The therapeutic armamentarium includes hyposensitization, antihistamines, decongestants, corticosteroids, antibiotics, avoidance of aspirin, control of diabetes, environmental manipulation, and surgery. Local recurrences, however, are not uncommon.

III. ANTROCHOANAL POLYPS

A. Introduction

The antrochoanal polyp (ACP), also known as the Killian polyp, is a large, solitary, typically unilateral polyp that arises in the maxillary sinus, usually on the posterior wall, occasionally on the inferior, medial, or lateral wall and rarely from the superior or anterior wall (1–6). It extends in an hourglass fashion through the normal or accessory ostium of the maxillary sinus into the middle meatus and then into the posterior choana where it accounts for 3% to 6% of all "nasal polyps" (2,7). In some instances, it may be large enough to obstruct the entire nasopharynx or even extend beyond the level of the soft palate.

Although some patients with ACPs have an allergic background, it is controversial whether this contributes to their formation (2–9). It is the consensus, however, that most are of an inflammatory rather than an allergic origin.

B. Clinical Features

ACPs are more common in males (65%) and in patients between 10 and 40 years of age (70%) (2–8). It accounts for 25% to 35% of all nasal polyps in children (9,10). Although rare instances of bilateral ACPs have been described, the overwhelming majority present as unilateral nasal obstruction associated with mouth breathing, snoring, rhinorrhea, protruding nasal mass, and/or recurrent episodes of sinusitis (6,11,12).

C. Imaging

The presence of a posterior choanal or nasopharyngeal soft-tissue density in conjunction with unilateral

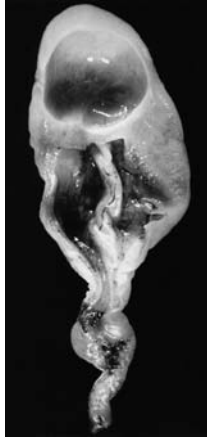


Figure 8 Antrochoanal polyp with large mucous retention cyst. Observe the long, tortuous tail.

mucosal thickening, cloudiness, or opacification of the maxillary sinus is highly suggestive of an ACP. Approximately 30% to 40% of patients, however, have bilateral maxillary sinusitis, but even in these instances, the polyp is almost invariably unilateral (2,3,7). ACPs do not erode or destroy contiguous soft tissue or bony structures (13). There is no significant lateralization to either maxillary sinus.

D. Pathology

Other than the presence of an occasional cyst, representing the maxillary component of the polyp, and the presence of a stalk or long pedicle, representing the maxillary attachment, ACPs are grossly identical with other nasal polyps (Fig. 8). Microscopically, there are only quantitative differences, at most, between the two; ACPs tend to have fewer mucoserous glands and fewer eosinophils than ordinary nasal polyps.

Atypical stromal cells, representing a reactive phenomenon, are sometimes seen. Their presence has no clinical significance, but pathologists should be aware of this finding so that they do not confuse the change with evidence of malignancy (Figs. 6 and 7) (14). Because of their long pedicle, ACPs are susceptible to torsion with compromise of their vascular supply resulting in histological changes that might be confused with a vascular neoplasm or even a malignant process. Such polyps are sometimes referred to as angiomatous or angiectatic ACPs (15,16).

E. Treatment and Prognosis

ACPs treated intranasally by snare and avulsion without due respect for their stalks have a 20% to 30% rate of recurrence; most of these reappear within two years of excision (2,3,7). If the maxillary sinus is entered and the pedicle of the polyp is removed with adjacent normal mucosa, the recurrence rate is practically nil.

IV. PRIMARY CILIARY DYSKINESIA (IMMOTILE CILIA SYNDROME)

A. Introduction

It is estimated that the human body contains about 3 trillion cilia, which are divided into eight categories: (i) mucus-propelling cilia, (ii) water-propelling cilia, (iii) nodal cilia, (iv) monocilia, (v) rudimentary cilia, (vi) olfactory cilia, (vii) photoreceptor cilia, and (viii) sperm flagella (1,2). Genetic errors of each result in specific outcomes. For example, defective water-propelling cilia, olfactory cilia, and sperm flagella may result in hydrocephalus, anosmia, and infertility, respectively.

The mucus-propelling cilia, the subject of the remaining discussion, are concerned with cleansing the upper and lower respiratory tract of particulate matter, noxious agents, and infectious organisms. Abnormalities of these are divided into two categories—primary and secondary. Primary causes are congenital or genetic and are typically associated with structural changes that render the cilia immotile and/or dysfunctional and predispose the individual to repeated episodes of rhinosinusitis, bronchitis, and/or pneumonia—a condition previously referred to as immotile cilia syndrome and, more recently, as PCD (3–9). Secondary causes (secondary ciliary dyskinesia) are acquired and are usually temporary and reversible. Such changes are seen in persistent heavy smokers and following viral infections of the upper respiratory tract (10,11).

B. Clinical Features

PCD occurs in 1 in 20,000 to 1 in 34,000 births and is not a life-threatening disease (1,6,12). Symptoms include rhinorrhea, a moist-sounding cough, rhinosinusitis often associated with polyps, bronchitis, and frequent ear complaints (otitis, decreased hearing). About half the cases are also associated with situs inversus or Kartagener's syndrome, an autosomal recessive disorder characterized by sinusitis, bronchiectasis, and situs inversus (13).

Although patients are symptomatic soon after birth ("my baby was born with a cold"), it is not unusual for some patients to be in adulthood before it is recognized. Once PCD is entertained, it is essential that cilia be evaluated for motility and ultrastructural abnormalities. Cilia from the nose, rarely the trachea, are usually obtained either by biopsy or brush technique (14).

C. Pathology

The mucus-propelling cilia are approximately 6 μ m in diameter and there are 200 or more per cell (2). They exhibit a characteristic 9 + 2 structure similar to the hubs and spokes of a wheel (Figs. 9 and 10). At the center are two singlet microtubules (representing the hub), which are connected to nine peripheral doublets (each representing two microtubules) by a series of nine spokes. The outer doublets are also

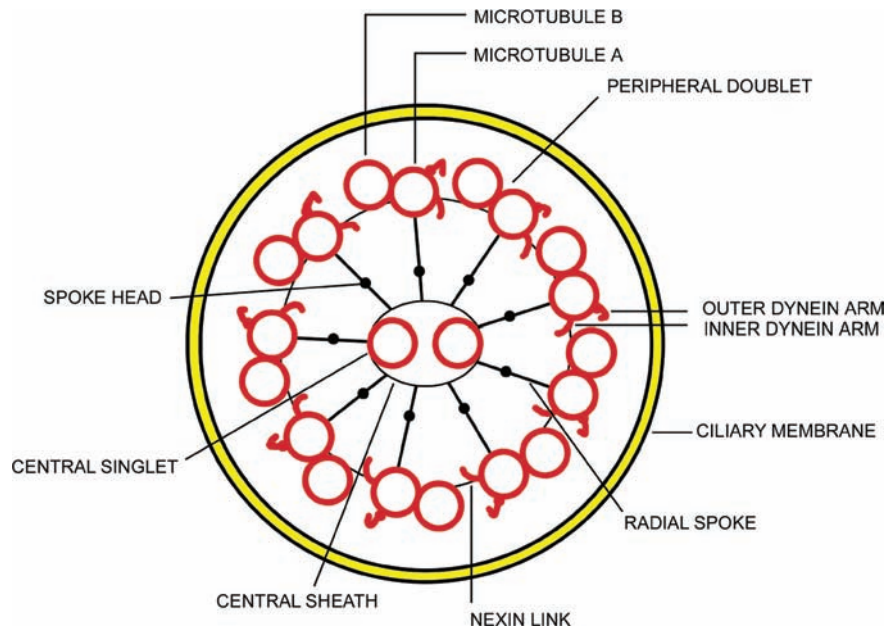


Figure 9 Cross-sectional diagram of a single cilium showing components and organization.

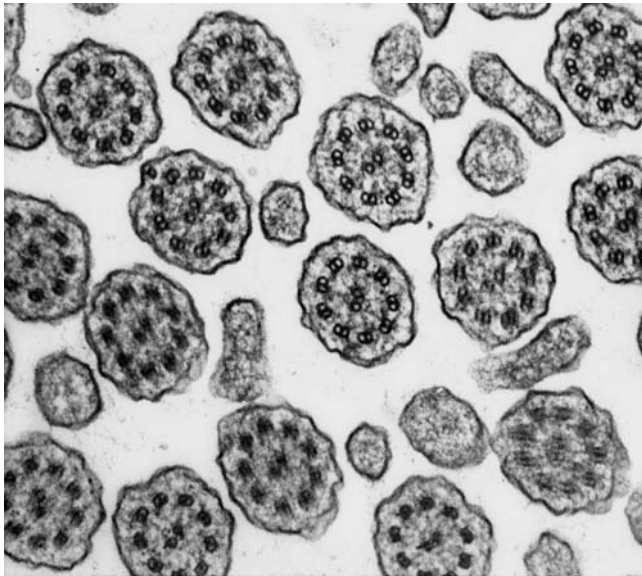


Figure 10 Electron microscopic view of normal nasal cilia obtained by brush microscopy. Compare with Fig. 9.

connected to one another by two arms, inner and outer dynein, that are attached to the doublets in a counterclockwise fashion. It is the arms that produce the actual motion (1). The cilia beat asymmetrically with a relatively stiff forward stroke to move the mucus, while on the backstroke they flex so that they are drawn through the mucus so as not to stir the mucus in the opposite direction.

Any loss of the structural units, as noted above, may result in immotile or dyskinetic cilia. The most common abnormalities are those of the dynein arms, either one or both are absent or diminished in number (2).

D. Treatment and Prognosis

As previously indicated, PCD is not a life-threatening illness. Treatment is palliative and centered around maintaining the airway with mucolytic agents and anti-inflammatory medication as needed. Obstructive nasal polyps may have to be removed and the sinuses drained. Serous otitis may also require myringotomies.

V. CYSTIC FIBROSIS

A. Introduction

CF (mucoviscidosis) is the most common lethal genetic disease among whites. It was first described by Franconi et al. in 1936 and was given its present name of CF by Anderson in 1938 (1,2).

The disease follows an autosomal recessive pattern of inheritance. A child born to two heterozygous carriers has a 1:4 risk of having the disease, a 1:2 chance of being a carrier, and a 1:4 chance of neither being a carrier nor having the disease. The disease does, however, vary among ethnic groups. It has the highest frequency among those of white Northern European extraction, affecting about 1:2000 to 1:2500 newborns in this population (3–6). The frequency of the heterozygote carrier in this same group is 1:20 to 1:25 (4,5). Blacks and Asians are seldom affected. Current estimates indicate that there are approximately

25,000 to 30,000 persons with this disease in the United States (6,7).

The gene responsible for CF has been localized to the long arm of chromosome 7 (4,8). This is a large gene composed of more than 250,000 base pairs and 27 exons that encodes for a protein of 1480 amino acids (4,6). This protein, referred to as cystic fibrosis transmembrane conductance regulator (CFTR), is intimately involved in a cAMP-dependent pathway for the transport of chloride across cell membranes (6,9).

The most common mutation in CF is a three-base-pair deletion that results in the absence of one amino acid (phenylalanine, abbreviated "F") in the 508 position of the CFTR protein (5,6). Except for the missing phenylalanine, the CFTR protein remains intact, yet the flaw changes its structure and function enough to produce a fatal disease. This specific genetic deletion, referred to as $\Delta F508$, occurs in approximately 70% of patients with CF and is associated with the most severe form of the disease (5,6,10). The remaining 30% of patients have mutations at any of more than 200 sites in the gene for CFTR (6).

The basic genetic abnormality in CF, in summary, is a defect in a cell membrane protein (CFTR) involved in the secretion and absorption of chloride. A decrease in chloride permeability across the membrane of epithelial cells of exocrine glands, in turn, leads to an influx of salt and water into the cells, resulting in dehydration of the extracellular fluid compartment, an increased chloride concentration in sweat (the basis of the diagnostic sweat test), and thickening of exocrine secretions.

B. Clinical Features

More than 60% of patients with CF will be diagnosed during the first year of life and fewer than 5% after the age of 15 years (6). Virtually, all of the clinical manifestations of the disease can be attributed to the thick, tenacious secretions that accumulate in the ducts of exocrine organs that lead to destructive, inflammatory changes, especially in the pancreas and lungs (11). Eighty-five percent to 90% of patients will experience pancreatic dysfunction with steatorrhea, malnutrition, and possible growth retardation. Pulmonary involvement, which tends to be chronic and suppurative, eventually leads to insufficiency, and this is the most common cause of death in patients with CF. Other manifestations include meconium ileus, cholelithiasis, biliary cirrhosis, and infertility.

The sinonasal tract is the most conspicuously involved site in the head and neck (12–18). Salivary glands are also affected, but rarely become symptomatic. Otitis media, likewise, is also uncommon in CF (19,20).

Sinus involvement in CF is initiated by accumulation of viscous secretions that block the draining ostia. This, in turn, leads to hypoxia, damage or functional loss of the ciliary-clearing mechanism, edema, inflammation, and colonization by bacteria, especially *Pseudomonas aeruginosa*, *S. aureus*, *H. influenzae*, or anaerobes (17).

Nasal polyps are common in patients with CF, with most large series reporting an incidence of 10% to 20% (range 6–48%) (11–13,15,21,22). The polyps tend to be multiple and bilateral and often appear at an early age. Nasal polyps in children are relatively uncommon; therefore, if a child develops bilateral nasal polyps before the age of 10 years, CF should always be considered. In a review of 120 children with nasal polyps, Schramm and Effron observed that 29% occurred in association with CF (23). However, polyps are rarely the first manifestation of CF. It is much more common for polyps to develop in patients with known CF (3).

Once the diagnosis is entertained, it can usually be verified by an elevated sweat chloride test in excess of 60 nEq/L. According to Davis, there are very few diseases in children that elevate the chloride concentration to this level (6). Among these are included untreated adrenal insufficiency, ectodermal dysplasia, renal diabetes insipidus, some forms of glycogen storage disease, and, possibly, untreated hypothyroidism. The role of molecular testing for the CFTR gene is also becoming more available (11,24,25).

C. Imaging

Imaging almost invariably reveals panopacification of the paranasal sinuses, particularly the maxillary and ethmoid. The frontal sinus is not present at birth and, in fact, often fails to develop in patients with CF (17). Despite evidence of radiographic involvement, only 11% to 57% of patients actually complain of symptomatic sinusitis (fever, purulent rhinorrhea, tenderness, or pain) (13,15). Bacterial colonization alone does not always lead to infection, but when infection occurs, it tends to be severe. Fortunately, the complications of sinusitis, such as osteomyelitis and orbital or cerebral abscesses, are rare (17). This may be the result of the frequent use of antibiotics or thickening of the adjacent bone from chronic persistent inflammation, which might prevent spread.

D. Pathology

There is controversy on whether or not nasal polyps removed from patients with CF show histological changes that are diagnostic of this disorder. Oppenheimer and Rosenstein indicate that nasal polyps associated with CF may be identified by a distinct triad of histological findings: (i) a thin delicate surface epithelial basement membrane, (ii) lack of extensive tissue eosinophilia, and (iii) the presence of acid mucin in the glands and cysts (acid mucin stains blue with the alcian blue–periodic acid–Schiff stain) (26). In contrast, polyps that are not due to CF, according to these investigators, exhibit a reversal of this triad: (i) a thick, hyalinized surface epithelial basement membrane, (ii) stromal eosinophilia, and (iii) the presence of neutral mucin in glands and cysts (neutral mucin stains red with alcian blue–periodic acid–Schiff stain).

Other investigators, on the other hand, contend that there are no significant histological differences between those polyps associated with CF and those that are not (3,12). More specifically, Tos et al. studied and compared 11 CF polyps with 102 non-CF polyps and found no difference in density, distribution, or architecture of glands, nor found any in the surface epithelium or stroma between the two types of polyps (12). From these studies, it is apparent that histological evaluation of nasal polyps in CF is not entirely specific and cannot be used alone to either establish or refute the diagnosis. However, the presence of neutrophils, sparse numbers of eosinophils, and lack of basement thickening in a nasal polyp removed from a child should make one at least think about CF.

The pathogenesis of nasal polyps in CF appears to be multifactorial. Some contend that they are clearly related to the thick mucus that distends the mucoserous glands. The cystic glands, in turn, compress adjacent blood vessels with subsequent stromal edema and prolapse (17,27). The incidence of allergic rhinitis is about the same in CF as in the general population (16). It is thought that allergy as well as infection may also contribute to the formation of some polyps in CF (12,17).

E. Treatment and Prognosis

Sinonasal disease in CF may respond to medical therapy, whereas others will require surgery. In the past, surgery was largely palliative and consisted primarily of simple polypectomy for nasal obstruction. Recurrences were high, but acceptable, because the risks associated with more extensive surgery and prolonged anesthesia were believed to be potentially life threatening. More recent studies, however, have not supported this viewpoint and clearly point to the advantages of combining polypectomy with additional sinus operations, such as the Caldwell-Luc procedure, endoscopic sinus surgery, or ethmoidectomy (13-16). Cepero et al., for instance, observed a 61% recurrence rate for patients who underwent nasal polypectomy alone versus 9% for those who had both polypectomy and additional paranasal sinus surgery (13).

Although there have been significant advances in the recognition and symptomatic treatment of CF, it continues to be a lethal disease, with a median survival of about 30 years (6). With the advent of lung transplantation and the possibility of gene therapy on the horizon, patients may live considerably longer or even be cured of their disease.

VI. ALLERGIC MUCUS—ALLERGIC FUNGAL RHINOSINUSITIS

A. Introduction

Fungal infections of the nasal cavity and paranasal sinuses can be divided into two broad categories: invasive and noninvasive (Table 4). Allergic fungal rhinosinusitis (AFRS), the newest member of the

Table 4 Classification of Fungal Infections of the Sinonasal Tract

I. Invasive
A. Acute, fulminant, immunocompromised
B. Chronic, indolent, immunocompetent
II. Noninvasive
A. Mycetoma: fungus ball
B. Allergic fungal rhinosinusitis

noninvasive group, is now being recognized with increased frequency.

AFRS represents about 5% to 10% of all cases of chronic sinusitis (1-5). It was probably first described in 1976 by Safenstein who reported a 24-year-old woman with allergic bronchopulmonary aspergillosis associated with nasal obstruction, nasal polyps, and nasal cast formation (6). Cultures of the sinus grew out *Aspergillus fumigatus*. In 1981, Miller et al. presented five additional cases and coined the phrase "allergic aspergillosis of the paranasal sinuses" (7). Katzenstein et al. reported seven more cases in 1983 and also noted that the fungal hyphae resembled those of *Aspergillus* and proposed the name "allergic *Aspergillus* sinusitis" (1). Subsequent reports revealed that fungi other than *Aspergillus* could also cause the syndrome and, accordingly, the more generic term of "allergic fungal sinusitis" was proposed (3,8-12).

More recently, it has been shown that allergic mucus is not unique to AFRS and that it can be seen in a variety of other eosinophilic sinonasal disorders [eosinophilic chronic rhinosinusitis (ECRS)], not necessarily of allergic origin (Table 5) (4,5,13,14). Accordingly, it has been proposed that the term "eosinophilic mucin" might be more accurate than "allergic mucus" (13).

Ponikau et al. have observed that fungal organisms can be demonstrated in almost all individuals, including normal controls as well as those suffering from chronic rhinosinusitis (15). Why some individuals develop an immunological reaction to the fungi and others do not is not entirely clear, but may be related to genetic factors and the atopic status of the patient.

The distinction between the various types of ECRS shown in Table 5 depends on clinical, physical, imaging, immunological, and pathological findings. So what is the role of the pathologist? The pathologist can only report the presence or absence of allergic (eosinophilic) mucus. If found, then he/she must report whether fungal organisms are seen and, if possible, try to identify the fungus. All too often, it is impossible for the pathologist to identify the fungal organisms with certainty, and as a result, a diagnosis

Table 5 Classification of ECRS

1. Superantigen-induced ECRS
2. Allergic fungal rhinosinusitis
3. Nonallergic fungal ECRS
4. Aspirin-exacerbated ECRS

Abbreviation: ECRS, eosinophilic chronic rhinosinusitis.
Source: From Ref. 14.

of “allergic (eosinophilic) mucus containing fungi of uncertain type” would be appropriate. It is then up to the clinician to determine whether the patient has AFRS or non-AFRS and, if necessary, the type of fungus with appropriate cultures. If the IgE level is elevated, he/she probably has AFRS and, if normal, nonallergic fungal ECRS (Table 5).

The following discussion pertains only to the AFRS.

B. Clinical Features

AFRS is currently defined as fungal organisms associated with allergic (eosinophilic) mucus and an elevated IgE (13,14).

AFRS should be suspected in any young adult who presents with (i) recurrent sinonasal polyps, (ii) a history of asthma, (iii) multiple involved sinuses on imaging, (iv) poor response to medical treatment, (v) a history of multiple surgical procedures for chronic polypoid sinusitis, and (vi) a history of atopy with sinonasal polyps, and (vii) who is found to have thick inspissated mucus at the time of surgical intervention (16).

AFRS affects both sexes equally and occurs in all age groups. Most, however, are between 20 and 40 years of age at the time of diagnosis. Virtually, all patients have sinonasal polyps, 41% have asthma, 70% have peripheral eosinophilia, 13% have a history of aspirin sensitivity, almost all have an increased serum total IgE level, and 52% to 58% have positive skin tests to fungal antigens (13).

C. Etiology

AFRS is thought to be mediated through a type I (IgE) and possibly type III (immune complex) immunological reaction. The disease begins by inhalation and trapping of the fungi in the mucous blanket of the sinonasal tract. Fungal antigens then react with IgE-sensitized mast cells with a subsequent cascade of immunological events that result in an inflammatory response.

D. Imaging

Computed tomography scans characteristically reveal opacification of the nasal cavity and one or more paranasal sinuses, either unilateral or bilateral (Fig. 11). Erosion of bone (skull base and orbit) is seen in 20% to 60% of cases and should not be mistaken for tumor (5,17–19). AFRS is almost always an isolated event; only rarely does it coexist with allergic bronchopulmonary aspergillosis.

E. Pathology

Pathologically, AFRS consists of edematous polypoid respiratory mucosa with numerous mononuclear inflammatory cells and prominent eosinophils. Hyalinization and thickening of the basement membrane and goblet cell hyperplasia with mucous

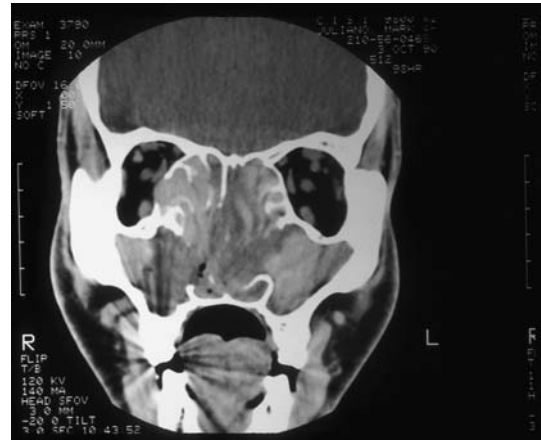


Figure 11 Image showing bilateral opacification of the nasal cavity and paranasal sinuses in a patient with allergic fungal rhinosinusitis. Note the erosion of bone, especially the medial wall of the right orbit.



Figure 12 Thick, tenacious mucus removed from a patient with allergic fungal rhinosinusitis, often described as similar to peanut butter or wet clay.

retention cysts are additional findings. The most distinguishing feature, however, is the character of the mucus that is grossly thick, white, yellow, green, or brown, with the consistency of “peanut butter” or “wet clay” (Fig. 12).

Microscopically, the mucus appears inspissated or “dried out” and purple or basophilic. It contains large collections of “smudged” eosinophils and neutrophils with admixed sloughed ciliated respiratory epithelial cells. At times, the mucus even appears laminated (Fig. 13). The eosinophils are frequently ruptured and their granules widely dispersed. Charcot-Leyden crystals are universal (Fig. 14). Fungi (hyphae), however, are sparse and, if found at all, are always located in the mucus and never in the tissue (Fig. 14). The use of fungal stains (silver methenamine and periodic acid-Schiff) are very useful.

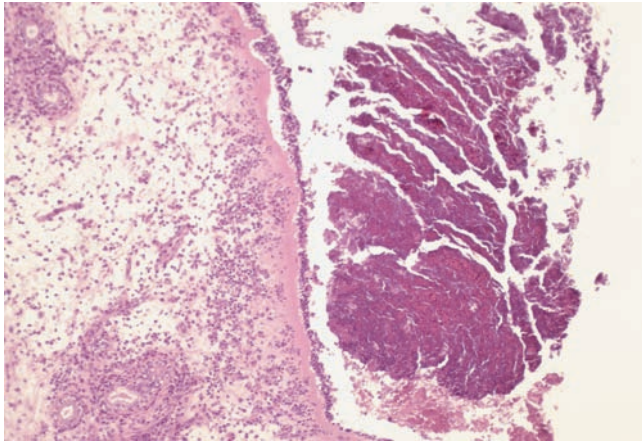


Figure 13 Note the edematous, inflamed respiratory mucosa with the thick, hyalinized basement membrane on the left and the allergic mucus on the right with a purple inspissated and laminated appearance with entrapped, degenerating inflammatory cells (H&E, 100 $\times$).

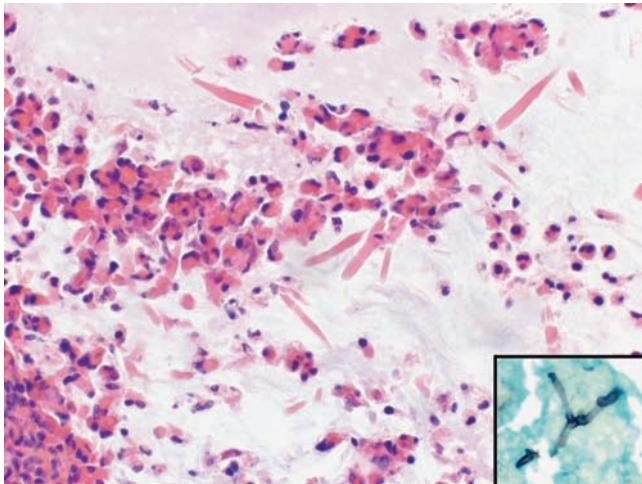


Figure 14 High-power magnification of allergic fungal rhinosinusitis. Note the Charcot-Leyden crystals and the degenerating eosinophils (H&E, 40 $\times$). A Grocott stain revealed a few fungal hyphae that were positive on culture for *Aspergillus* (inset, Grocott, 400 $\times$).

Mucus with the foregoing characteristics is referred to as "allergic (eosinophilic) mucus." Fungi are not always demonstrated histologically or by culture in patients who have allergic mucus. In fact, in about 35% to 40% of patients with allergic mucus, no fungi will be found (3). The failure to demonstrate fungi might be related to tissue sampling or to destruction of the fungus by the existing inflammation. Alternatively, allergens or conditions other than fungal may be responsible for the allergic mucus (Table 5).

Caution must be exercised in trying to identify fungi by their characteristics in tissue sections. Cultures have shown that many of the septated hyphal forms observed in biopsies are actually dematiaceous or other fungi mislabeled as *Aspergillus*. In a review of cultures from 139 patients with "AFRS," Cody et al. observed that the cultures were positive in 63% of patients and negative in 37% (3). Of those with positive cultures, the most commonly recovered fungi, in descending order, were *Bipolaris*, *Curvularia*, *Aspergillus*, and *Alternaria*.

The Fontana-Masson stain may be very helpful in distinguishing some of the dematiaceous fungi from an *Aspergillus* sp. The former group of fungi produces a melanin-like pigment and, accordingly, will be positive with this stain. *Aspergillus* sp., with the exception of *Aspergillus niger*, will be negative.

F. Treatment and Prognosis

The treatment of patients with allergic mucus is the same, regardless of the presence or absence of fungi. This consists of complete endoscopic removal of the mucus and inflamed tissue followed by intranasal or systemic corticosteroids and possible maintenance therapy with fungal desensitization vaccines (5,11,16,20,21). Since the fungus is noninvasive, systemic antifungal agents are not indicated. There is, however, some evidence that topical antifungal agents or irrigating the sinonasal tract with a solution of these drugs may be beneficial by decreasing the numbers of fungi and, thereby, lessening the antigenic stimulus.

Persistence of disease is common, particularly when there has been incomplete eradication of the allergic mucin. Even when the patient is disease-free, recurrences are possible, presumably from reexposure to fungal antigens.

VII. MUCOCELES

A. Introduction

A mucocoele of a paranasal sinus is a slowly enlarging, epithelial-lined lesion, containing mucus. It fills the sinus cavity and, if neglected, may erode bone and involve contiguous structures. The mucus is usually sterile, but secondary infection may lead to the development of a mucopyocoele.

Any condition that obstructs the draining ostium of a sinus can lead to a mucocoele. Among the various causes are included inflammation, allergies, previous surgery, trauma, or tumor. The distribution and frequency of mucocoeles among the sinuses vary according to medical center (Table 6) (1-7). All agree, however, that the frontal sinuses are more often involved.

Mucocoeles are typically unilateral and limited to one sinus. Some, however, do involve two or more sinuses. When multiple, the sinuses most often affected are the frontoethmoid and sphenothmoid (8-11).

Table 6 Distribution of Mucocoeles of the Paranasal Sinuses

Sinus	Bockmuhl (7) (N = 290)	Natvig (1) (N = 112)	Total (%) (N = 402)
Frontal	125	86	211 (52%)
Maxillary	72	3	75 (19%)
Ethmoid	41	7	48 (12%)
Sphenoid	29	0	29 (7%)
Frontoethmoid	23	16	39 (10%)

B. Clinical Features

Mucocoeles occur over a broad age range, but are uncommon in children. Most patients are between 40 and 70 years of age (1). The gender distribution varies from 1:1 to 2:1 in favor of males (1,7).

Signs and symptoms depend on the involved sinus but usually include headache, pain or pressure over the sinus, nasal obstruction, periorbital swelling, exophthalmos, and disturbances of vision and smell. About 10% of individuals are asymptomatic.

Exceptional cases of sphenothmoid mucocoeles have been associated with amenorrhea and galactorrhea (11). Some mucocoeles are “invasive” and may extend into the orbit or anterior cranial cavity (8,10).

C. Imaging

Imaging studies show a normal or expanded sinus with a diffuse, homogenous opacification. One or more bony walls may appear thin or eroded (12,13). If the mucocoele is related to previous surgery, imaging will reveal “footprints” of the prior procedure. Rarely, gross calcific deposits may also be seen (14).

D. Pathology

The diagnosis of a mucocoele of a paranasal sinus is a clinical and not a histological diagnosis. Characteristic imaging studies and the finding at surgery of a sinus filled with mucus associated with a narrow ostium is diagnostic.

The specimen sent to pathology consists only of the lining of the mucocoele—ciliated respiratory mucosa—and no mucus. As a result, it is impossible for the pathologist to determine whether the lining is simply normal mucosa, represents a case of rhinosinusitis, or is the wall of a mucocoele.

The ciliated respiratory lining may exhibit increased inflammatory and goblet cells, focal squamous metaplasia, ulceration, granulation tissue, loss of cilia, and/or thickening and hyalinization of basement membranes (9,15).

E. Treatment and Prognosis

Treatment consists of surgically evacuating the mucus content of the mucocoele and reestablishing adequate drainage of the sinus. This can usually be accomplished with an endoscope (7,16). Local recurrences are rare and usually do not exceed 2% (7).

VIII. CHOLESTEROL GRANULOMA

A. Introduction

CGs are relatively frequent in the middle ear–mastoid but distinctly unusual in the paranasal sinuses. Most originate in the maxillary sinus, but any sinus can be involved (1–6). They may also arise in the orbital bones, especially the frontal bone in the region of the superotemporal quadrant above the lacrimal fossa. Most orbitofrontal CGs, however, remain separate from the frontal sinus but may on occasion involve the sinus (7,8).

B. Etiology

Hemorrhage, impaired drainage, and poor ventilation are important etiological factors. Prior trauma and severe episodes of chronic rhinosinusitis with mucosal ulceration are thought to be the sources of bleeding. Leon et al. have also suggested that increased intra-sinus pressure due to drainage obstruction may affect venous and lymphatic drainage from the sinus cavity leading to venule microhemorrhages while still allowing arterial blood in the sinus mucosa and further contributing to a larger localized hemorrhage (3).

Subsequent hemolysis of the blood leads to the accumulation of cholesterol from the red blood cells and an inflammatory giant cell reaction known as CG.

C. Clinical Features

CGs are more common in men and occur over a broad age range (26–65 years) with a mean age of 42 years (1–6). They typically develop in patients with a history of chronic rhinosinusitis or trauma. Signs and symptoms are largely nonspecific, and, as a result, the diagnosis is rarely suspected clinically. The most frequent complaints are headache, facial pain or pressure, nasal congestion, periorbital swelling, visual disturbances, dysosmia, and even otalgia. Proptosis is almost universal in patients with orbitofrontal CGs (7).

D. Imaging

Imaging studies are nonspecific and range from polypoid mucosal thickening to opacification of the sinus. Occasionally, one will see an expanding cyst-like lesion with erosion and/or destruction of one or more of the bony walls, which may, in some instances, masquerade as a malignant neoplasm (4).

E. Pathology

The gross appearance varies according to the duration of the lesion. Some are bloody and resemble a liquefied hematoma, while others are more fibrotic, yellow to golden brown.

Microscopically, a CG consists of a more or less circumscribed mass of inflammatory granulation and/or fibrous tissue containing numerous elongated clefts surrounded by foreign body giant cells. The

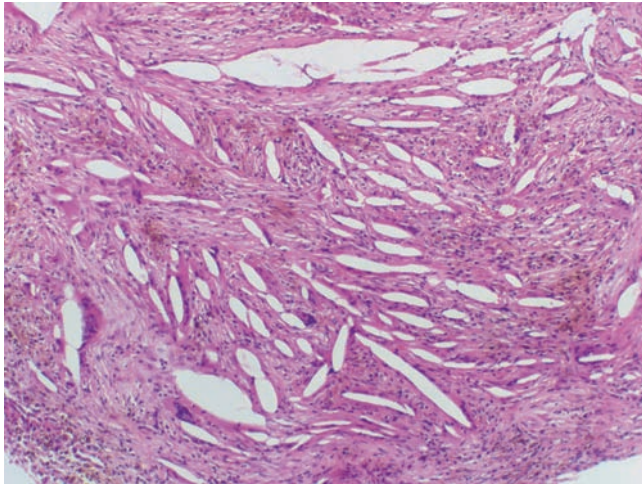


Figure 15 Cholesterol granuloma composed of granulation-fibrous tissue containing cholesterol clefts, hemosiderin, inflammatory cells, and giant cells (H&E, 700 $\times$).

clefts represent the footprints of cholesterol crystals dissolved in tissue processing. Hemosiderin is always present, and there may be evidence of recent hemorrhage (Fig. 15).

F. Treatment and Prognosis

Surgical excision, usually through a Caldwell–Luc procedure, with restoration of drainage and ventilation is the treatment of choice.

IX. MYOSPHERULOSIS

Myospherulosis is basically an iatrogenic pseudomycotic disease caused by the interaction of red blood cells with petrolatum, lanolin, or traumatized human adipose tissue (1–8). As a result, large, sporangium-like sacs filled with numerous spherules are produced that are often mistaken for a fungus. However, these structures do not react with the usual fungal stains, do not grow in cultures, and are not compatible with any known pathogenic fungus. Tissue removed from these patients contains microscopic pseudocysts that, when numerous, impart a Swiss cheese appearance. The pseudocysts are surrounded by dense fibrous tissue containing lymphocytes, plasma cells, histiocytes, and multinucleated foreign body giant cells (Fig. 16). Within these spaces, one finds large, brown, sac-like structures (“parent bodies”) containing numerous endobodies (“spherules”) (Fig. 16). The parent bodies are generally round, have a thick non-refractile wall, and range from 20 to 120 μ m in diameter (2). Budding yeasts, hyphae, or pseudohyphae are not seen. The structures do not react with methenamine silver or periodic acid–Schiff stains. They also give negative staining reactions for cellulose and chitin, indicating that they are not inhaled pollen

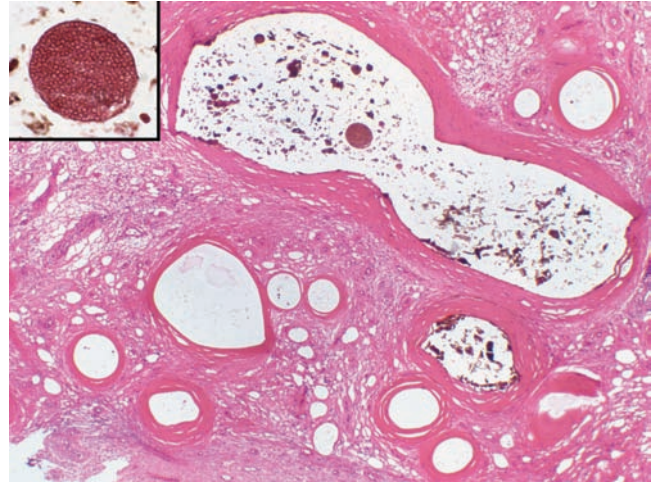


Figure 16 Myospherulosis. Note the pseudocysts surrounded by dense fibrous tissue with scattered inflammatory cells (H&E, 40 $\times$). Some of the pseudocysts contain altered erythrocytes that agglomerate into sporangium-like sacs that may be mistaken for a fungus (*inset*, H&E, 400 $\times$).

grains, an observation that has been confirmed by electron microscopy (2,9).

The disease was first described in 1969, when McClatchie et al. reported a series of seven patients from East Africa suffering from solitary, indurative soft-tissue lesions of the arms, legs, and buttocks (10). Unable to classify the fungus-like bodies present in biopsies of these patients, they coined the descriptive term “myospherulosis” for this disease. The disease was not recognized in the United States until 1977, when Kyriakos described 16 patients from the St. Louis metropolitan area (2). However, in contrast to the African patients, those in St. Louis had their disease confined to the nose, paranasal sinuses, and middle ear. The patients, eight men and eight women ranging from 15 to 86 years of age, all had previous operations, usually a Caldwell–Luc procedure, involving these areas of the body. The operations were performed for inflammatory conditions and a variety of benign and malignant tumors. Kyriakos astutely observed that at the termination of each of the surgical procedures, the wound was packed with gauze impregnated with petrolatum and an antibiotic (usually tetracycline). He suggested that contaminated gauze might be the source of the myospherules.

Rosai, intrigued by the resemblance of the endobodies to erythrocytes, observed that these structures were positive when stained for hemoglobin and peroxidase (3). Furthermore, he noted that when erythrocytes were incubated with a petrolatum-tetracycline ointment, typical parent bodies with spherules were formed. These observations clearly established the erythrocyte origin of the myospherules and laid to rest the notion of an infectious disease. Wheeler and McGavran subsequently demonstrated that either petrolatum or lanolin, both components of the ointment,

and not the antibiotic, were the culprits responsible for the disease (4). In addition, they found that emulsified human fat could also induce formation of these structures and offered this as an explanation for the disease in the African patients. Reasoning that it was unlikely that all the African patients had been exposed to antibiotic ointments, they suggested that fat necrosis secondary to trauma, injections, or infections might result in lipids responsible for the formation of myospherules.

Although myospherulosis was initially thought to be a totally innocuous iatrogenic disorder, subsequent reports have indicated that it may exceptionally occur spontaneously (11,12) and, in many instances, often results in a chronic, painful inflammatory reaction that requires surgical removal (13). The excised tissue is fibrotic and often has a brown or black discoloration from acid hematin, a degradation product of hemoglobin (5,14).

Myospherulosis must be recognized to avoid confusion with mycotic disease and the attendant morbidity of unwarranted antifungal therapy. The diseases most often confused with this disorder are coccidioidomycosis and rhinosporidiosis. In contrast with myospherulosis, these two organisms are positive with the usual fungal stains and are negative on immunostaining for hemoglobin. Furthermore, *Rhinosporidium* is mucicarminophilic, whereas myospherulosis is not. Reports describing the synchronous occurrence of both myospherulosis and *Aspergillus* sp., however, have been published (15).

X. EOSINOPHILIC ANGIOCENTRIC FIBROSIS

A. Introduction

Eosinophilic angiocentric fibrosis (EAF) is a chronic, idiopathic disorder that characteristically involves the upper respiratory tract, especially the nasal cavity, which leads to progressive obstruction and airway compromise over a course of many years (1–15).

The disease was first described by Holmes and Panje in 1983 who regarded it as an intramucosal form of granuloma faciale (1). It was Roberts and McCann, who in 1985, reported three more cases, described the pathology in detail, and coined the term “eosinophilic angiocentric fibrosis” (2).

B. Etiology

The etiology is unknown. Whether EAF represents a mucosal form of the cutaneous lesion known as granuloma faciale or whether it has any relationship at all to this lesion remains uncertain. Some patients have a history of allergic rhinosinusitis or allergies to other substances, such as penicillin. This coupled with the fact that large numbers of eosinophils are observed in tissue samples have led some to speculate that EAF may have an allergic basis. On the other hand, most patients do not have allergies, and corticosteroids, thus far, are largely ineffective in controlling the disease. These features mitigate against allergy as an etiological factor.

C. Clinical Findings

In our review of 23 cases, 13 occurred in females and 10 in males who ranged in age from 25 to 79 years (mean 50 years) (1–15). The disease most often involves the nasal cavity, either unilaterally or bilaterally, and only rarely extends into the sinuses (usually the maxillary) or orbit (6,14,15). At least two cases have been described in the subglottic area of the larynx (2,3). In the nasal cavity, the preferred site is the septum followed by the lateral wall. As the disease evolves, usually over many years, the nasal cavity becomes progressively obstructed and multiple sites are involved.

Nasal obstruction is, by far, the most frequent initial complaint. Pain and epistaxis are uncommon.

On physical examination, the nasal mucosa and adjacent soft tissue appear swollen, thickened, and fibrotic, often resulting in fibrous tumor-like masses. In more advanced cases, the entire nose may be enlarged and deformed.

At least 4 (17%) of the 23 cases reviewed were found to have cutaneous lesions of granuloma faciale (1,2,8,11). These appeared on the skin of the nose, malar prominence, temporal area, and forehead. In two cases, the cutaneous lesions predated the appearance of EAF, while the other two developed during the course of the disease.

D. Imaging

Imaging studies show thickening or polypoid hyperplasia of the nasal mucosa and soft tissue often associated with opacification of one or more sinuses and deviation of the nasal septum. Destruction of cartilage and bone is not uncommon in more advanced cases.

E. Pathology

Roberts and McCann have identified two phases of the disease, early (active) and late (quiescent), which may coexist (2). The active phase is characterized by a prominent inflammatory infiltrate composed of numerous eosinophils with admixed plasma cells, lymphocytes, and few neutrophils centered around capillaries, venules, and arterioles (Fig. 17). The inflammatory cells may spill into the walls of blood vessels, but vascular necrosis and thrombosis are rare to absent. Small foci of stromal necrosis, however, may be seen. Multinucleated giant cells and granulomas are not observed.

In the late stage, the inflammation becomes less intense and fibrosis more apparent. The most characteristic feature of the disease, in addition to eosinophils, is the prominent deposition of collagen around blood vessels in an “onion skin” pattern (Fig. 18). Even in the late stage, eosinophils are still usually apparent, unless the patient has received prior corticosteroids.

The spindle cell fibrotic areas demonstrate diffuse strong positivity for vimentin but are negative for smooth muscle actin, desmin, S-100 protein, and

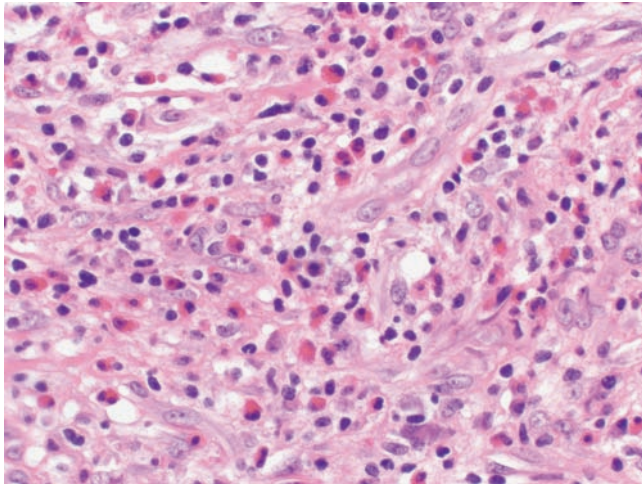


Figure 17 Eosinophilic angiocentric fibrosis, early phase. Note the prominent component of eosinophils (H&E, 400 $\times$).

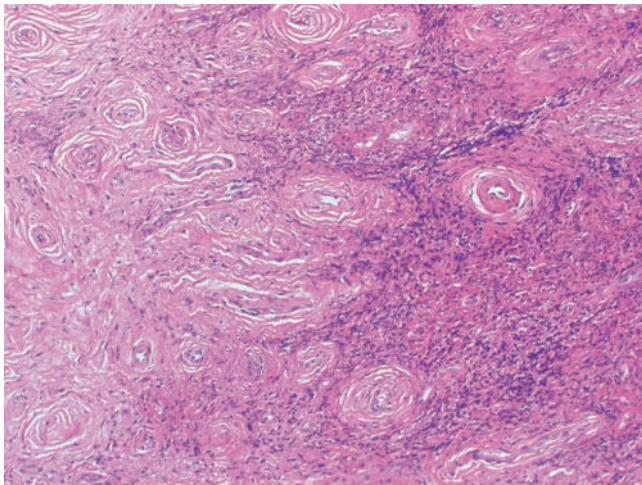


Figure 18 Eosinophilic angiocentric fibrosis, late phase. The small blood vessels are surrounded by rings of collagen ("onion-skin" pattern), and fibrosis is more apparent (H&E, 400 $\times$).

CD-34 (6). The inflammatory infiltrate is polyclonal, reacting with B- and T-cell markers without a specific pattern of distribution and without light chain restriction (6).

Complete blood counts show no evidence of peripheral eosinophilia. Antineutrophil cytoplasmic autoantibodies (ANCA) are negative, and the erythrocyte sedimentation rate is normal or only slightly elevated.

F. Differential Diagnosis

The differential diagnosis includes Wegener's granulomatosis, Churg-Strauss syndrome, and inflammatory

pseudotumor. The absence of multinucleated giant cells, granulomas, prominent (geographic) necrosis and peripheral eosinophilia, and negative cytoplasmic-staining antineutrophil cytoplasmic autoantibodies (c-ANCA) and perinuclear-staining antineutrophil cytoplasmic autoantibodies (p-ANCA) are sufficient to exclude the first two conditions. Inflammatory pseudotumor typically does not contain large numbers of eosinophils nor shows the typical "onion skinning" of blood vessels.

G. Treatment and Prognosis

Surgery is the treatment of choice. Although largely untested, initial results indicate that corticosteroids and cytotoxic agents are ineffective. Recurrences over a course of many years are common, necessitating repeat excisions.

XI. RESPIRATORY EPITHELIAL ADENOMATOID HAMARTOMA

A. Introduction

Hamartomas (from the Greek, *hamartia*, meaning "fault" or "defect") are benign, nonneoplastic overgrowths of tissue(s) indigenous to the area of their occurrence. They may be composed entirely of epithelial or mesenchymal elements or both and should be distinguished from teratomas and dermoids (1–5). Teratomas are composed of tissues from all three germ layers and are capable of autonomous growth, whereas dermoids are usually cystic and comprise primarily of ectodermal and, to a lesser extent, mesodermal elements.

B. Clinical Features

Hamartomas of the sinonasal tract are uncommon and most often of the pure epithelial type. Wenig and Heffner have described 31 cases composed of a benign glandular proliferation of respiratory epithelial cells that they have designated as "respiratory epithelial adenomatoid hamartomas (REAH)" (4).

These occurred in 27 men and 4 women who ranged in age from 27 to 81 years (median 58 years). Most were unilateral and arose from the nasal cavity (22 cases, 71%), particularly the posterior nasal septum and, to a lesser extent, along the lateral nasal wall, middle meatus, and inferior turbinate. A few, however, were bilateral. The remaining cases occurred in the nasopharynx and paranasal sinuses. Nasal stuffiness, obstruction, epistaxis, and chronic rhinosinusitis with or without coexistent nasal polyps were the most common manifestations.

C. Pathology

REAHs are typically polypoid or exophytic, rubbery, tan-white to red-brown and range up to 6 cm in greatest dimension (2,4) (Fig. 19). Histologically, they are composed of small-to-medium-sized, round-to-oval

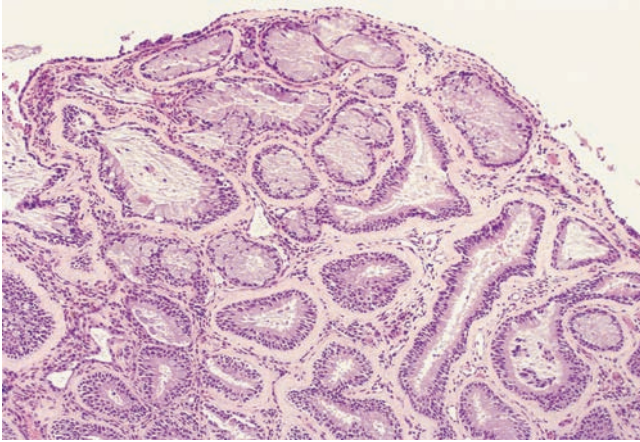


Figure 19 Respiratory epithelial adenomatoid hamartoma composed of small to medium-sized glands lined by ciliated, respiratory epithelium (H&E, 100 $\times$).

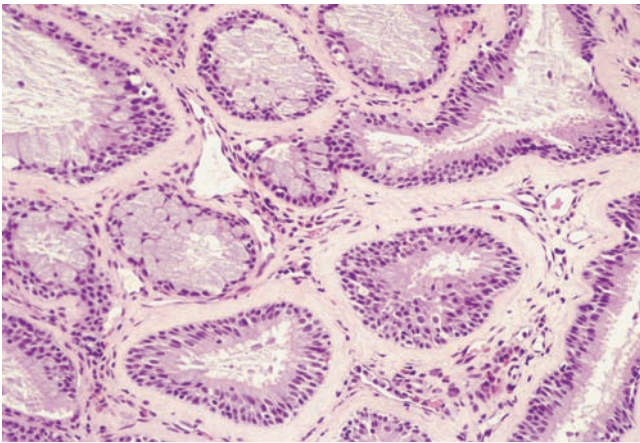


Figure 20 Higher magnification of respiratory epithelial adenomatoid hamartoma. Note that each gland tends to be surrounded by a thick eosinophilic or hyalinized basement membrane (H&E, 200 $\times$).

glands lined by ciliated respiratory epithelium, often with numerous, admixed mucin-secreting (goblet) cells. The glands arise from invagination of the surface epithelium into the lamina propria and, consequently, often maintain direct continuity with the surface. The glands are widely spaced and characteristically surrounded by thick, eosinophilic basement membranes (Fig. 20). The stroma is well vascularized, edematous, or fibrous and contains scattered chronic inflammatory cells.

Small mucoserous (salivary) glands are also occasionally seen. Whether they are part of the hamartoma or just a reactive hyperplastic response to the inflammation is uncertain, although the latter is favored (4).

Hamartomas composed entirely of mucoserous glands (1) and mesenchymal components (2,3,5) have also been described in the sinonasal tract.

D. Differential Diagnosis

REAHs are most often confused with ordinary nasal polyps, inverted papilloma (IP), and adenocarcinoma. The presence of excess glands readily distinguish this lesion from a nasal polyp. In contrast with REAH, which occurs primarily on the nasal septum, IPs arise almost exclusively on the lateral nasal wall in the vicinity of the middle turbinate and ethmoid sinus area. IPs are also composed predominantly of hyperplastic islands of squamous epithelium with few interspersed mucous (goblet) cells and a prominent intraepithelial component of neutrophils. Respiratory epithelium may also be seen, but is usually not dominant. The basement membranes around the epithelial islands in IPs are also thin and delicate, not thick and hyalinized, as seen in REAH. Mucoserous glands are also sparse to absent in IPs.

Adenocarcinomas are characterized by back-to-back arrangement of their glands, occasional nuclear pleomorphism, prominent mitotic activity, and a desmoplastic response to stromal invasion. These features are not seen in REAH.

E. Treatment and Prognosis

Simple but complete surgical excision is curative. Recurrences are practically nonexistent.

XII. SCHNEIDERIAN PAPILLOMAS

A. Introduction

The ectodermally derived, ciliated, respiratory mucosa that lines the nasal cavity and paranasal sinuses, so-called Schneiderian membrane, gives rise to three morphologically distinct papillomas. These are referred to individually as the exophytic, inverted, and oncocytic Schneiderian papillomas or, collectively, as Schneiderian papillomas.

Ever since their first recognition by Ward in 1854, papillomas of the sinonasal tract have been the center of controversy over their nomenclature, etiology, pathology, and biological behavior (1). Over the years, no fewer than 53 different terms have been applied to these lesions. It was Hyams who, in 1971, finally brought some order to this chaos when he reported the clinicopathological features of 315 Schneiderian papillomas and proposed that they be subclassified into the three types, as basically noted above (2). There are some, however, who still consider these three lesions as a single entity and group them together under such generic terms as "papilloma," "papillomatosis," or "Schneiderian papilloma" (3,4). We, as well as others, are firmly convinced that there are sufficient clinical, pathological, and potential etiological differences among these lesions to warrant their separation (5,6).

As a group, Schneiderian papillomas are uncommon, representing only 0.4% to 4.7% of all sinonasal tumors (7). Nasal polyps, in turn, are 25 to 60 times more common than papillomas (3,8).

Although the etiology is unsettled, a viral origin, at least for the exophytic papilloma (EP) and IP, has been suggested. This issue is discussed in more detail later. An association with allergy, inflammation, smoking, or other environmental noxious agents is not convincing (2,9).

Although Fu et al. have reported a series of nine patients with Schneiderian papillomas, who also had a personal history of genital warts, it is generally conceded that patients with sinonasal papillomas do not exhibit an increased tendency for developing papillomas in other sites (10).

B. Exophytic Papilloma (Fungiform Papilloma, Septal Papilloma, Squamous Papilloma)

Clinical Features

Depending on the series, EP comprise 18% to 50% of all Schneiderian papillomas (Table 7) (2,5,11,12). They are 2 to 10 times more common in men and occur primarily in individuals between 20 and 50 years of age (range 21–87 years) (2,13). They characteristically arise on the nasal septum, usually the anterior portion; only 4% to 21% originate on or involve the lateral nasal wall (2,14,15). Involvement of the paranasal sinuses is distinctly unusual, if indeed, it occurs at all. There is no significant lateralization to either side of the nose. Generally solitary and discrete, they may be multifocal, but bilaterality is rare (3.6%) (13). Epistaxis, nasal obstruction, or the presence of an asymptomatic mass are the typical presenting symptoms.

On physical examination, EPs appear as exophytic, papillary, or warty gray, pink, or tan, non-translucent growths attached to the nasal septum by a relatively broad base (Fig. 21).

Etiology

There is increasing evidence to suggest that EPs may be etiologically related to the human papillomavirus (HPV), especially types 6 and 11, rarely 16 and 57b. In a collective review of 79 EPs evaluated for the presence of HPV by in situ hybridization or the polymerase chain reaction, 45 (57%) were positive (Table 8) (10,11,15–21).

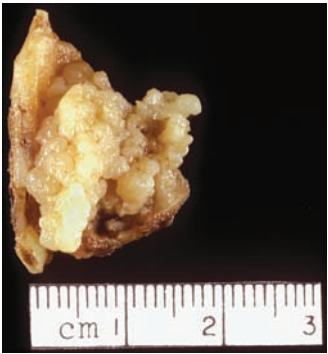


Figure 21 Exophytic papilloma attached to the nasoseptal cartilage by a broad base.

Imaging

Imaging evaluation of EP is generally not indicated. At most, the lesion will appear as a soft-tissue density along the nasal septum, with little, if any, evidence of nasal septal erosion.

Pathology

Most EPs range from a few millimeters up to about 2 cm. Microscopically, they are composed of papillary fronds with delicate fibrovascular cores covered by epithelium, 5- to 20-cells thick, that varies from squamous to transitional (intermediate) to ciliated, pseudostratified columnar (respiratory) (Fig. 22). Scattered mucin-containing cells, representing residual goblet cells, are common. Surface keratinization is absent or scant, unless the patient is a “nose picker” and irritates the lesion or if the papilloma is unusually large and hangs into the nasal vestibule where it is more exposed to the drying effect of ambient air. In these instances, surface keratin may be apparent. Mitoses are rare and never atypical. The fibrovascular stroma contains few, if any, mucoserous glands and, unless infected or irritated, sparse inflammatory cells.

Carcinoma and Exophytic Papilloma

Carcinoma arising in or associated with EPs is exceptional. Buchwald et al. have described a case of a 40-year-old man who developed a squamous cell carcinoma in an EP that was first excised 16 years ago (23). HPV 6/11 was demonstrated by in situ

Table 7 Frequency of Various Types of Schneiderian Papillomas

References	Total no. of cases	No. of exophytic papillomas	No. of inverted papillomas	No. of oncocytic Schneiderian papillomas
Hyams (2)	315	156 (50%)	149 (47%)	10 (3%)
Buchwald (11)	78	16 (21%)	57 (73%)	5 (6%)
Michaels (5)	191	36 (19%)	139 (73%)	16 (8%)
Weiner (12)	114	21 (18%)	90 (79%)	3 (3%)
Total	698 (100%)	229 (33%)	435 (62%)	34 (5%)

Table 8 Incidence of HPV in Exophytic Papillomas

References	Test	Total no. of cases	Total no. positive for HPV	Percent positive	Type(s) of HPV
Hirschfield (16)	DNA-ISH	10	7	70	6/11
Judd (17)	DNA-ISH, PCR	3	3	100	6/11
Fu (10)	RNA-ISH	5	4	80	6/11
Kashima (18)	PCR	26	4	15	6,11
McLaughlin (19)	DNA-ISH, PCR	5	3	60	6/11
Sarkar (20)	PCR	2	1	50	6b/11
Wu (21)	RNA-ISH, PCR	7	7	100	57b
Buchwald (11)	DNA-ISH, PCR	16	11	69	6/11, 16
Gaffey (22)	DNA-ISH, RNA-ISH	5	5	100	6, 11
Total		79 (100%)	45 (57%)	Average = 72% Median = 70% Range = 15–100%	

Abbreviations: DNA-ISH, deoxyribonucleic acid in situ hybridization; RNA-ISH, ribonucleic acid in situ hybridization; PCR, polymerase chain reaction; HPV, human papillomavirus.

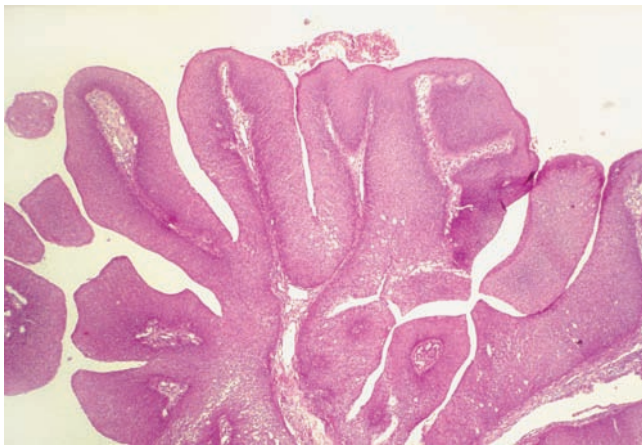


Figure 22 Exophytic papilloma composed of papillary fronds of squamous cells. Note the absence of surface keratin and scattered foci of clear cells within the epithelium, which represent residual mucous cells (H&E, 40×).

hybridization and polymerase chain reaction in the original papilloma as well as in the recurrent papilloma and in the carcinoma.

Norris described another possible case that occurred in a 62-year-old man who experienced four recurrences of his EP over the course of nine years (13). He subsequently developed an invasive squamous cell carcinoma in the same area.

Differential Diagnosis

EP must be distinguished from the much more common keratinizing cutaneous papillomas (e.g., verruca vulgaris) occurring in the nasal vestibule. The lack of extensive surface keratinization and the presence of mucous cells (accentuated by mucin stains) and ciliated or “transitional” epithelium serve to distinguish EP from cutaneous papillomas. In addition, the presence of mucoserous glands and septal cartilage further indicate that the lesion is of mucosal, rather than cutaneous origin.

Treatment and Prognosis

Complete surgical excision is the treatment of choice. Because the majority of recurrences tend to occur in the site of previous removal, inadequate excision, rather than multiplicity of lesions, probably accounts for most of the 22% to 50% incidence of local recurrence (2,8,13).

C. Inverted Papilloma

Clinical Features

IPs constitute 47% to 79% of all Schneiderian papillomas (Table 7). They are two to five times more common in men and are found primarily in the 40- to 70-year age group (2,3,9,14,15,24–31). The six-year-old boy included in the series of Eavey is the youngest patient yet described with the disease (32).

They characteristically arise from the lateral nasal wall in the region of the middle turbinate or ethmoid recesses and often extend secondarily into the sinuses, especially the maxillary and ethmoid and, to a lesser extent, the sphenoid and frontal. Isolated lesions of the paranasal sinuses without nasal involvement, however, do occur (31,33). Only about 8% of IPs arise on the nasal septum (34). Their rarity on the nasal septum may be partly due to the fact that there is little soft tissue in the septum for the lesion to invert into before it meets the resistance of the underlying septal cartilage which, in turn, would force the lesion to grow exophytically.

Although reported to be bilateral in 0% to 10% of cases, such an occurrence should always arouse the suspicion of septal erosion and perforation from unilateral disease (2,3,15,25,30).

Exceptionally, IPs may arise in sites other than the sinonasal tract. They have been recorded in the oropharynx (35), posterior pharyngeal wall (36), hypopharynx (37), nasopharynx (35,38), lacrimal sac (39), middle ear-mastoid (40), and possibly in the wall of a branchial cleft cyst (41). It has been suggested that ectopic migration of the Schneiderian membrane during embryogenesis could account for those aberrant papillomas in sites contiguous with the sinonasal tract

(2). Whether all of these ectopic cases are bona fide IPs is uncertain.

Unilateral nasal obstruction is the most common presenting symptom. Other manifestations include nasal drainage, epistaxis (10–20% of cases), anosmia, headaches (especially frontal), epiphora, proptosis, and diplopia. Pain, on the other hand, is an uncommon initial complaint, occurring in only about 10% of cases. When present, it should always suggest secondary infection or even a malignant change (25).

On physical examination, IPs present as pink, tan, or gray nontranslucent, soft-to-moderately firm polypoid growths, with a convoluted or wrinkled surface (Figs. 23 and 24).

Etiology

Although IPs have long been suspected of being of viral origin, viral inclusions have never been unequivocally demonstrated by either light or electron microscopy. In addition, they are almost invariably negative when stained for the HPV by immunoperoxidase. Some investigators, however, have demonstrated

HPV genomes in IPs by in situ hybridization or the polymerase chain reaction, particularly HPV 6 and 11, sometimes 16 and 18, and exceptionally HPV 57. The frequency of finding the virus by these specialized techniques is highly variable, ranging anywhere from 0% to 100% (Table 9) (10,11,16–21,42–52). In a collective review of 341 IPs evaluated for the presence of HPV by a variety of sophisticated molecular techniques, 131 (38%) were positive (Table 9).

Macdonald et al. have also found evidence of the Epstein-Barr virus (EBV) DNA in 13 of 20 (65%) IPs by using the polymerase chain reaction and have raised the possibility that this virus might be involved in its pathogenesis (53). Gaffey et al., on the other hand, in an in situ hybridization study of 19 IPs (1 of which was associated with squamous cell carcinoma) found no evidence of EBV (22). Obviously, more studies are needed to resolve these conflicting data and the relation, if any, between IPs and EBV.

If one assumes that the IPs is etiologically related to the HPV, then several important questions need to be addressed: (i) Why is the virus so site specific (i.e., lateral nasal wall)? (ii) Why are IPs almost invariably unilateral? (iii) Why are IPs so rare in children who are, conceivably, more susceptible to viral infections than adults? (iv) If the IP is related to an HPV infection, why do we not see several members of a family affected with the lesion? (e) If due to HPV, could IPs be treated with antiviral medication, rather than by surgery?

Imaging

Imaging findings vary with the extent of the disease (54). Early on, there may be only a soft-tissue density within the nasal cavity or paranasal sinuses. Later, with more extensive disease, unilateral opacification and thickening of one or more of the sinuses are common, as are expansion and displacement of adjacent structures (Fig. 25). Pressure erosion of bone may also be apparent and must be distinguished from osseous invasion associated with malignancy. Extensive bone destruction should always raise the possibility of a carcinoma arising in, or associated with, an IP.

Pathology

Microscopically, IPs are composed of hyperplastic ribbons of basement membrane—enclosed epithelium that grows endophytically into the underlying stroma (Figs. 26 and 27). The epithelium is multilayered, usually 5- to 30-cells thick, and formed of squamous or ciliated, columnar (respiratory) epithelial cells admixed with goblet cells. Nonkeratinizing squamous epithelium tends to predominate, but occasionally a case may be composed almost entirely of respiratory epithelium (Figs. 28 and Fig. 29). Gradations between these two extremes are not uncommon, resulting in a transitional epithelium reminiscent of that seen in the urinary tract. All of these epithelial types may be present in the same lesion, and their proportions may vary widely in different lesions or even in

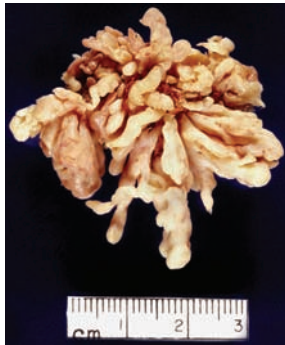


Figure 23 Gross appearance of an inverted papilloma of the lateral nasal wall removed intact by a medial maxillectomy. Note the polypoid growth and that each papillary structure is opaque and will not transilluminate.

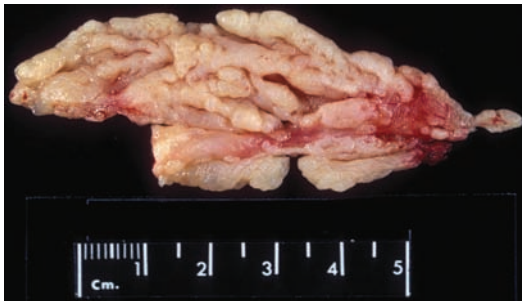


Figure 24 Gross appearance of an inverted papilloma. Note the convoluted surface, much like the gyri and sulci of the brain or a wrinkled prune.

Table 9 Incidence of HPV in Inverted Papillomas

References	Test	Total no. of cases	Total no. positive for HPV	Percent positive	Type(s) of HPV
Respler (42)	Southern blot	2	2	100	11
Syrjanen (43)	IP-PAP, DNA-ISH	14	11	79	11, 16
Weber (44)	DNA-ISH	21	16	76	6b, 11
Brandwein (45)	RNA-ISH	7	5	71	6/11, 16/18
Bryan (46)	PCR	13	10	77	6, 11
Klemi (47)	DNA-ISH	19	13	68	11, 16
Siivonen (48)	DNA-ISH	21	13	62	11, 16
Hirschfield (16)	DNA-ISH	9	2	22	6/11
Ishibashi (49)	Southern blot	7	1	14	6
Furuta (50)	Dot blot, ISH, PCR	26	5	19	11, 16
Judd (17)	DNA-ISH, PCR	9	0	0	0
Fu (10)	RNA-ISH	4	4	100	6/11
Kashima (18)	PCR	29	7	24	6, 11
McLachlin (19)	DNA-ISH, PCR	17	4	24	6, 11, 16
Sarkar (20)	PCR	24	0	0	0
Wu (21)	RNA-ISH	15	12	80	57, 16
Beck (51)	PCR	32	20	63	6, 11, 16, 18
Buchwald (11)	DNA-ISH, PCR	52	3	6	6, 11
Ogura (52)	Southern blot	1	1	100	57
Gaffey (22)	DNA-ISH, RNA, ISH	19	2	11	11, 16
Total		341 (100%)	131 (38%)	Average = 50% Median = 62.5% Range = 0–100%	

Abbreviations: DNA-ISH, deoxyribonucleic acid in situ hybridization; RNA-ISH, ribonucleic acid in situ hybridization; PCR, polymerase chain reaction; IP-PAP, immunoperoxidase antiperoxidase; HPV, human papillomavirus.



Figure 25 Image of a 46-year-old man with an inverted papilloma. There is a soft-tissue density in the area of the left middle turbinate (arrow) associated with opacification of the left frontal, ethmoid, and maxillary sinuses.

different areas of the same papilloma (Fig. 30). Mitoses are not numerous and, if present at all, are seen primarily in the basal and parabasal epithelium.

Ten percent to 20% of IPs may show focal surface keratinization and 5% to 20% varying degrees of dysplasia (2,9,24,51,55,56). These are not necessarily signs of malignancy, but they should alert the pathologist of the need for thorough evaluation of the papilloma.

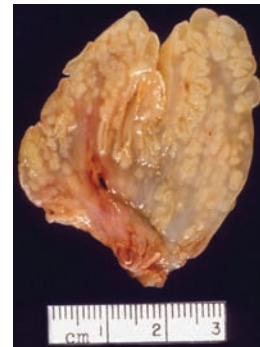


Figure 26 Cut surface of an inverted papilloma. Note the hyperplastic ribbons of epithelium that grow inward into the stroma.

The stroma ranges from dense and fibrous to loose and myxoid, with or without an inflammatory component (Fig. 27). The inflammatory cells, especially neutrophils, often transmigrate through the epithelium (Fig. 29). Eosinophils and basement membrane thickening are not seen (Figs. 28 and 29). Mucoserous glands are also sparse to absent because the abnormal epithelium uses the salivary ducts and glands as scaffolds to extend into the stroma, thereby obscuring their normal appearance.

As IPs enlarge, they may obstruct the drainage of nearby sinuses. As a result, it is not uncommon to also find ordinary nasal polyps in IP specimens. They can usually be identified grossly by their more myxoid

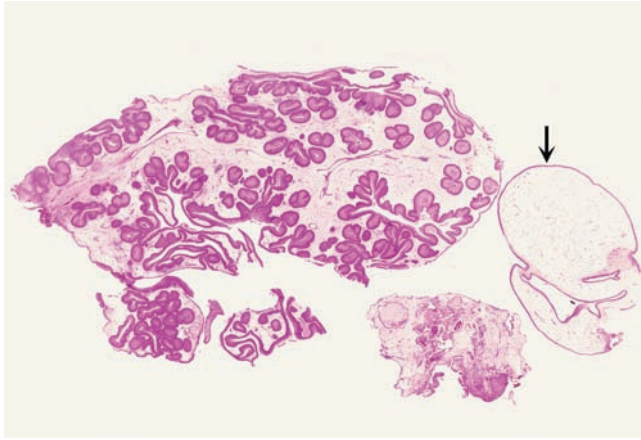


Figure 27 Patient with concurrent inverted papilloma and a nasal polyp (*arrow*). Polyps are smooth, glistening, mucoid to myxoid, and transilluminant. Because of the mass effect of the epithelium growing inward, inverted papillomas will not transilluminate.

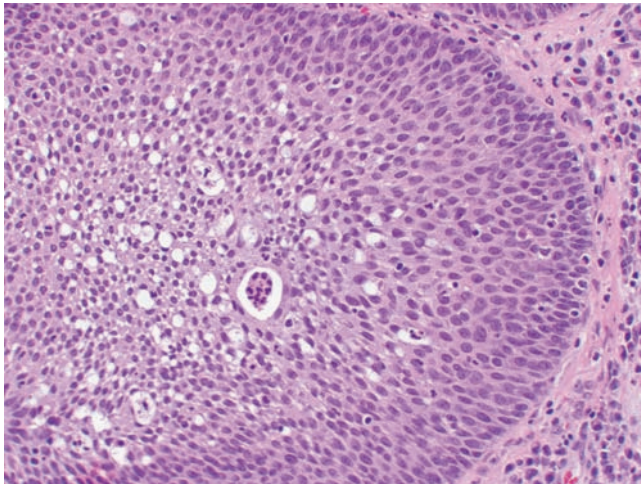


Figure 28 Higher magnification of the advancing (inverted) edge of an inverted papilloma. The epithelium is of the squamous type and the clear cells are mainly due to the accumulation of glycogen. Note the thin basement membrane and sharp boundary between epithelium and stroma (H&E, 200 $\times$).

appearance and the fact that they will transilluminate, whereas IPs will not (Fig. 27).

Rarely, an IP will exhibit focal surface changes reminiscent of a verruca vulgaris; that is, it will show focal papillary squamous epithelial hyperplasia, with marked keratosis or parakeratosis, with or without a prominent granular cell layer, and often contains numerous vacuolated cells suggestive of koilocytes (Fig. 31). Although this might be a viral effect, immunohistochemical stains for HPV, in my experience, are invariably negative. When this change is observed, the

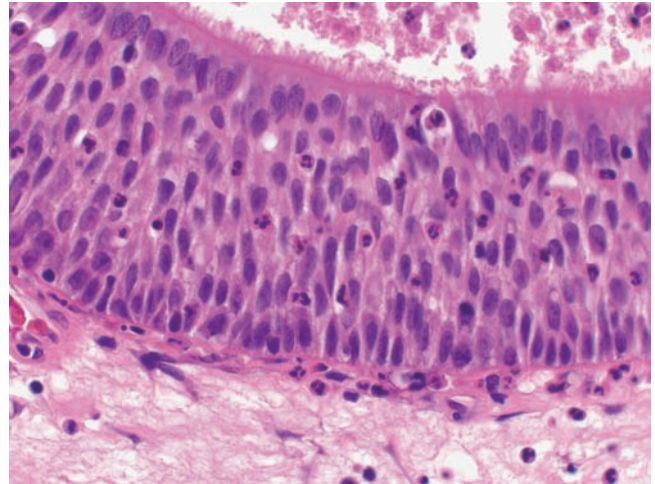


Figure 29 Inverted papilloma composed of hyperplastic ciliated respiratory epithelium. Observe the thin basement membrane and characteristic epithelial transmigration of neutrophils (H&E, 400 $\times$).

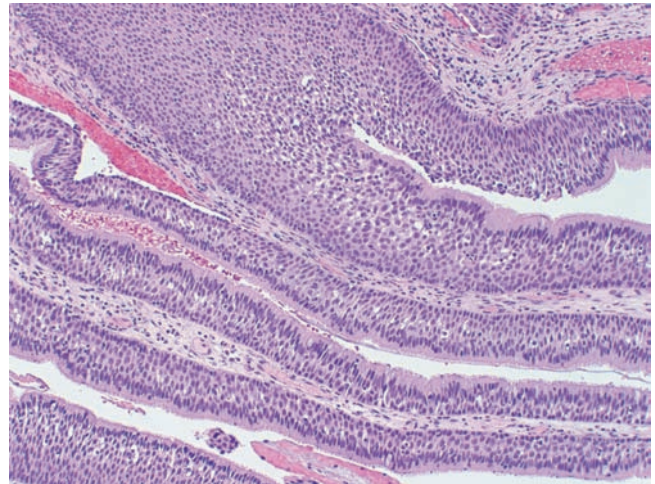


Figure 30 Inverted papilloma composed of squamous and ciliated respiratory epithelium (H&E, 100 $\times$).

diagnosis of “IP with focal verrucous hyperplasia” might be appropriate. This change has no clinical significance other than it might be mistaken for a verrucous carcinoma (see sect. “Differential Diagnosis”).

Carcinoma and Inverted Papilloma

IPs are occasionally complicated by carcinomas, especially squamous cell carcinoma and, to a much lesser extent, verrucous (57,58), mucoepidermoid (3), spindle cell, and clear cell carcinomas (8), as well as adenocarcinoma (54). The incidence of malignant change in individual series of IPs has ranged

anywhere from 2% to 27% (Table 10) (2–4,9,11,14, 26–31,47,51,55,56,59–62). In a collective review of 1390 IPs reported in the literature, 150 (11%) were associated with carcinoma (Table 10).

Patients with IPs that are associated with carcinomas fall into three groups: (i) those who have

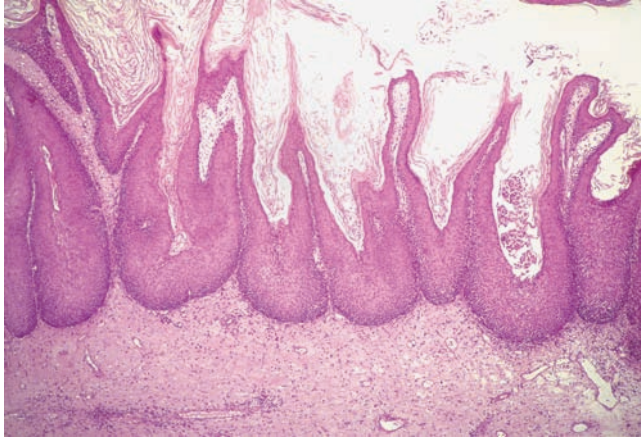


Figure 31 Inverted papilloma with focal verrucous hyperplasia. Note the papillary epithelial hyperplasia and marked surface keratinization. Although not illustrated, a prominent granular cell layer and koilocytes are also occasionally seen. This change may be mistaken for a verruca vulgaris or a verrucous carcinoma (H&E, 40×).

primarily an IP with only a small focus of carcinoma, (ii) those who have primarily a carcinoma with only a small focus of IP, and (iii) those who have an IP and then years later develop a carcinoma in the area in which the papilloma arose.

Of all carcinomas associated with IPs, approximately 61% are synchronous and 39% metachronous (Table 10). For metachronous carcinomas, Lesperance and Esclamado observed the mean interval between the onset of the IP and the development of carcinoma to be 63 months (range 6 months–13 years) (63).

Carcinomas complicating IP vary from well- to poorly differentiated and exhibit a broad range of behavior. Some are in situ and of little consequence, whereas others are locally aggressive or may even metastasize (Fig. 32).

The carcinomas may actually arise within the papilloma (carcinoma ex-IP), as evidenced by a gradation of histological changes, ranging from dysplasia, to carcinoma in situ, to frankly invasive carcinoma; whereas in others, the carcinoma is merely associated with a histologically bland IP. Once a carcinoma is recognized, the pathologist should not only indicate the histological type, the degree of invasion and differentiation, and the adequacy of resection margins (if possible) but also quantitate its volume (e.g., the specimen consists of 30% IP and 70% poorly differentiated squamous cell carcinoma).

There is no correlation between the number of local recurrences of an IP and the subsequent development of carcinoma (25). There is some evidence, however, to suggest that HPV 16 and 18 may be more

Table 10 Incidence of Carcinoma in Inverted Papillomas

References	Total no. of inverted papillomas	No. of carcinomas	No. of carcinomas		Percent of carcinoma
			Synchronous	Metachronous	
Norris (55)	29	2	1	1	7
Skolnik (59)	33	5	1	4	15
Hyams (2)	149	19	?	?	13
Snyder (3)	39	8	7	1	21
Lasser (60)	17	4	2	2	24
Woodson (61)	90	4	1	3	4
Abildgaard-Jensen (56)	21	3	2	1	14
Weissler (4)	223	11	8	3	5
Segal (62)	30	3	0	3	10
Christensen (14)	39	7	6	1	18
Klemi (47)	19	3	2	1	16
Phillips (27)	112	8	8	0	7
Myers (26)	33	7	5	2	21
Outzen (28)	67	1	0	1	2
Furuta (50)	26	7	5	2	27
Dolgin (29)	42	5	4	1	12
Bielamowicz (30)	61	10	5	5	16
Vrabec (9)	101	8	7	1	8
Beck (51)	39	10	3	7	26
Buchwald (11)	57	5	3	2	9
Lesperance (63)	51	14	6	8	27
Lawson (31)	112	6	4	2	5
Total	1390	150 (11%)	80 (61%)	51 (39%)	Average = 14% Median = 13.5% Range = 2–27%

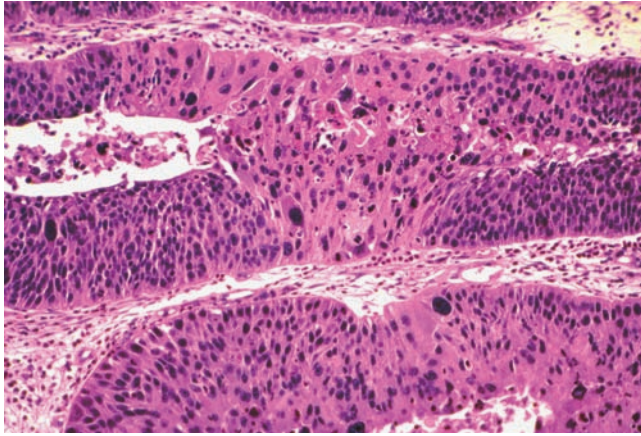


Figure 32 Inverted papilloma with focal squamous cell carcinoma in situ. Note the pleomorphic cells and intact basement membrane (H&E, 200 $\times$).

carcinogenic than HPV 6 and 11 (47,48,51). In the study of Klemi et al. and Siivonen and Virolainen (47,48), three of eight (38%) IPs that contained HPV 16 also had carcinoma. Klemi et al. also studied 19 IPs by flow cytometry (47). Six of 19 (32%) were aneuploid and of the six that were aneuploid, two (33%) were associated with carcinomas. Only 1 of the 13 (8%) diploid IPs was associated with carcinoma. They indicated that if the papillomas were both HPV 16-positive and aneuploid, the incidence of malignant transformation was even higher.

According to Schwerer et al., p53 expression as determined by immunohistochemistry can be detected in the majority of IPs, but usually only in the basal and parabasal cells (64). Strong diffuse staining, however, is associated with a sixfold greater chance for carcinoma (65).

Data also suggest that CD44s may also be useful in predicting which IP will become malignant. Ingle et al. observed that CD44s is diffusely expressed immunohistochemically in typical IPs, whereas an IP with an invasive squamous cell carcinoma, the expression of CD44s in the malignant component is reduced or absent (66).

In a molecular-genetic appraisal of IPs, Califano et al. confirmed that the papillomas are monoclonal proliferations but are not necessarily premalignant (67). They concluded that "IPs do not fit the profile of a prototypic precursor lesion in that they do not harbor critical genetic alterations that are known to drive malignant transformation of the upper respiratory tract. In some instances, concurrent IPs and sinonasal squamous cell carcinoma may even arise from entirely different progenitor cells."

Differential Diagnosis

The differential diagnosis includes nasal polyps with squamous metaplasia, respiratory epithelial adenomatoid hamartoma, inverted ductal papilloma

(IDP) of minor salivary gland origin, and invasive carcinoma.

In nasal polyps with squamous metaplasia, one will usually see thickening and hyalinization of the basement membrane, prominent mucoserous glands and, often, a large number of inflammatory cells, especially eosinophils. These features are absent in IP. In addition, the epithelium lining the mucoserous glands in nasal polyps is not multilayered, contains more mucous cells, and does not show the characteristic epithelial transmigration of neutrophils.

Features that are useful in distinguishing respiratory epithelial adenomatoid hamartoma from IP are covered elsewhere in this chapter (see sect. "Respiratory Epithelial Adenomatoid Hamartoma"). Although IDP and IP share similar names, they should not be confused. The former is innocuous compared with the potentially locally aggressive behavior of the latter. In contrast with IP, which arises from the surface epithelium and grows endophytically, IDP arises from the excretory duct of minor salivary glands; hence, it will grow intraluminally and be confined by the duct. IP also arises in the sinonasal tract, while the IDP occurs almost exclusively in the oral cavity.

Invasive carcinoma can be distinguished from the ordinary IP by the presence of the following features in the former lesion and their absence in the latter: cellular pleomorphism, atypical mitoses, keratin pearls, loss of basement membrane, and unequivocal invasion associated with an inflammatory desmoplastic stromal response.

Treatment and Prognosis

IPs are thought to enlarge by squamous metaplasia of the adjacent mucosa. Although histologically benign, they have an unlimited growth potential and, if neglected, can cause considerable morbidity or even death by extending into contiguous structures (68). Attempts to remove these lesions intranasally by snare and avulsion have resulted in "recurrence (persistence?)" rates of 0% to 74% (average 60%) (31) (Fig. 33).

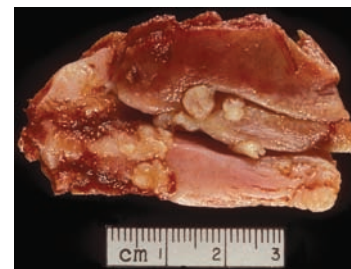


Figure 33 Patient with an inverted papilloma of the lateral nasal wall that was initially treated by a conservative intranasal approach. Because of recurrence (?persistence), a medial maxillectomy was necessary for complete removal. Note the random small foci of residual papilloma on the turbinates.

Table 11 Krouse Staging System for Inverted Papilloma

T1	Tumor totally confined to the nasal cavity, without extension into the sinuses. The tumor can be localized to one wall or region of the nasal cavity or can be bulky and extensive within the nasal cavity, but must not extend into the sinuses or into any extranasal compartment. There must be no concurrent malignancy.
T2	Tumor involving the ostiomeatal complex, ethmoid sinuses, and/or the medial portion of the maxillary sinus, with or without involvement of the nasal cavity. There must be no concurrent malignancy.
T3	Tumor involving the lateral, inferior, superior, anterior, or posterior walls of the maxillary sinus, with or without involvement of the medial portion of the maxillary sinus, the ethmoid sinuses, or the nasal cavity. There must be no concurrent malignancy.
T4	All tumors with any extranasal/extrasinus extension to involve adjacent, contiguous structures such as the orbit, the intracranial compartment, or the pterygomaxillary space. All tumors associated with malignancy.

Source: From Ref. 70.

The “gold standard” of therapy for most IPs has been a lateral rhinotomy and medial maxillectomy with meticulous removal of all mucosa in the ipsilateral paranasal sinuses (26,57). With this approach, the incidence of recurrence is 20% (range 0–37%) (69). More recently, a less aggressive approach using endoscopic resection has gained momentum. With this technique and proper patient selection, the incidence of recurrence is 12% (range 0–33%) (69). The choice of therapy depends on the training and bias of the surgeon, extent of tumor, and possibility of coexistent malignancy. To compare therapeutic modalities, Krouse has proposed a staging system for IPs, which involves the use of both CT-MRI imaging and endoscopic examination (Table 11) (70).

Although surgery is, and should remain, the primary treatment modality for IP, Mendenhall et al. have suggested (71) that radiation therapy may have merit in a small subset of patients with advanced or incompletely resected tumors. Radiation therapy should also be considered as an adjunct in patients who have carcinomas arising in IPs.

Recurrences typically appear within two to three years of therapy but, in some instances, are delayed for many years. Attempts to correlate histological features with risk of recurrence have been unsuccessful (2,31,55,72). Even those with prominent mitotic activity or dysplasia do not invariably show an increased incidence of recurrence or malignancy. Nevertheless, dysplasia, especially if moderate to severe, demands thorough microscopic evaluation of all resected tissue to avoid overlooking small foci of cancer.

Whether the demonstration of HPV in IPs is associated with a greater risk of local recurrences is also open to debate. Beck et al. noted (51) that patients whose IP contained HPV often developed relapses, whereas Furuta et al. found (50) no relation between HPV infection and local recurrence.

D. Oncocytic Schneiderian Papilloma (Cylindrical Cell Papilloma, Columnar Cell Papilloma)

Clinical Features

Oncocytic Schneiderian papilloma (OSP) is the rarest of the three morphological variants of Schneiderian papillomas, constituting only 3% to 8% of the total (2,5,11,12,73–75) (Table 7). It shows many features in common with the IP. In fact, some consider it to be only a variant of the IP. Microscopically, however, the two lesions are distinct.

OSP is equally distributed between the sexes and most of the patients are older than 50 years at the time of diagnosis. The youngest patient reported thus far in the literature has been a 33-year-old woman (76). Recently, however, I have seen a case in consultation that involved a 25-year-old woman.

OSP occurs exclusively on the lateral nasal wall or in the sinuses, usually the maxillary or ethmoid, and presents as a fleshy pink, tan, red-brown, or gray papillary or polypoid growth (Fig. 34). Unilateral nasal obstruction and intermittent epistaxis are the most common symptoms.

Etiology

At least 22 cases of OSPs have been examined by in situ hybridization or the polymerase chain reaction for the presence of HPV, and all have been negative (11,16,17,20,22) (Table 12). This is in contrast with the exophytic and IPs in which HPV has been found in many instances. Although this may be a sampling problem, it does raise the possibility that the OSP is not etiologically linked to this virus.

Imaging

The imaging features are identical with those of the IP described in the foregoing section.



Figure 34 Gross appearance of oncocytic Schneiderian papilloma. Note both the exophytic (white arrow) and inverted growth (black arrow).

Table 12 Incidence of HPV in Oncocytic Schneiderian Papillomas

References	Test	Total no. of cases	Total no. positive of HPV	Percent positive	Type(s) for HPV
Hirschfield (16)	DNA-ISH	2	0	0	0
Judd (17)	DNA-ISH, PCR	3	0	0	0
Sarkar (20)	PCR	9	0	0	0
Buchwald (11)	DNA-ISH, PCR	5	0	0	0
Gaffey (22)	DNA-ISH, RNA-ISH	3	0	0	0
Total		22	0	0	0

Abbreviations: DNA-ISH, deoxyribonucleic acid in situ hybridization; RNA-ISH, ribonucleic acid in situ hybridization; PCR, polymerase chain reaction; HPV, human papillomavirus.

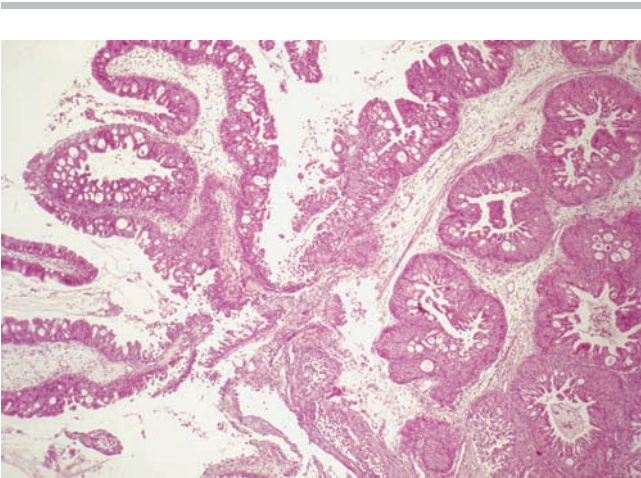


Figure 35 Oncocytic Schneiderian papilloma showing both exophytic and inverted patterns of growth (*left and right* sides of illustration, respectively) (H&E, 40 $\times$).

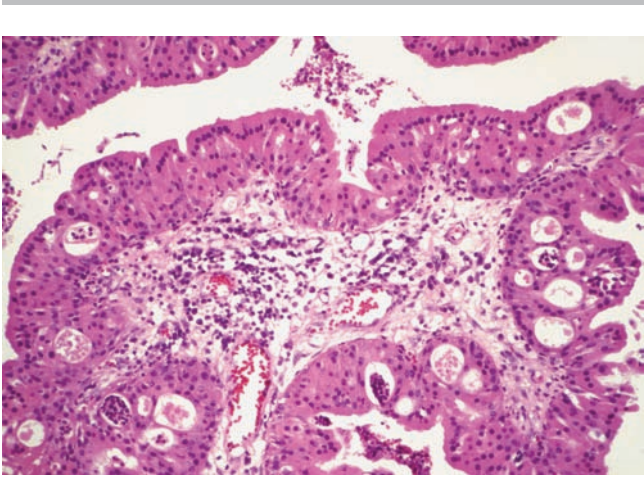


Figure 36 Oncocytic Schneiderian papilloma. Note the multi-layered oncocytic epithelium, numerous intraepithelial mucin-filled cysts, and microabscesses (H&E, 200 $\times$).

Pathology

Microscopically, OSP exhibits both exophytic and endophytic patterns of growth (Fig. 35). The epithelium is multilayered, two- to eight-cells thick, and is composed of tall columnar cells, with swollen, finely granular cytoplasm reminiscent of oncocytes (Figs. 36 and 37). Barnes and Bedetti have shown that the cells not only resemble oncocytes but also possess a high content of cytochrome-*c* oxidase and ultrastructurally are distended with mitochondria, thus clearly establishing their oncocytic character (73). The nuclei are either small, dark, and uniform or slightly vesicular, with barely discernible nucleoli. Cilia in varying stages of regression may be observed in a few of the outermost cells.

The epithelium characteristically contains numerous small cysts filled with mucin or neutrophils (microabscesses) (Figs. 36 and 37). The stroma varies from edematous to fibrous and may contain modest numbers of lymphocytes, plasma cells, and neutrophils, but few eosinophils. Mucoserous glands are sparse to absent.

Carcinoma and Oncocytic Schneiderian Papilloma

Approximately 4% to 17% of all OSPs may harbor a carcinoma (2,73,77,78). Most of these are squamous,

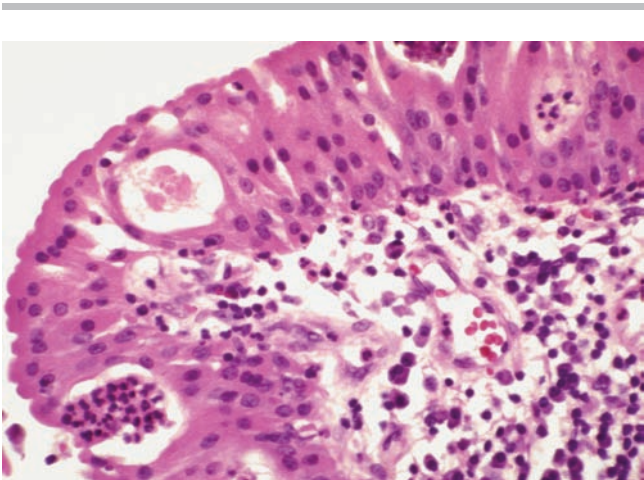


Figure 37 Higher magnification of the oncocytic Schneiderian papilloma shown in Figure 36 (H&E, 400 $\times$).

but mucoepidermoid, “transitional,” sinonasal undifferentiated and small cell carcinomas have also been described (77–79).

As in IP, the carcinoma complicating OSP may actually arise within the papilloma as evidenced by a

gradation of histological changes, ranging from dysplasia, to in situ, to invasive carcinoma, or it may merely be associated with the OSP. Prognosis depends on the histological type, degree of invasion, and the extent of tumor. In some instances, the carcinoma is in situ and of little consequence to the patient, whereas others are locally aggressive and may even metastasize.

Differential Diagnosis

The intraepithelial mucin-filled cysts, because of their spheroidal nature and mucicarminophilia, are often mistaken for rhinosporidiosis. In rhinosporidiosis, however, the organisms are not only limited to the epithelium but also involve the stroma and, moreover, never induce a diffuse oncocyctic change in the epithelium. The OSP is also occasionally mistaken for a low-grade papillary adenocarcinoma. The presence of intact basement membranes, the lack of nuclear pleomorphism and mitotic activity, and the absence of extensive bone destruction on imaging are features that point to the benignity of the tumor. Furthermore, the stratified oncocyctic epithelium of an OSP is in distinct contrast to the single-layered, nononcocyctic epithelium seen in a low-grade adenocarcinoma.

Treatment and Prognosis

The clinical behavior parallels that of the IP. Effective treatment consists of a lateral rhinotomy and medial maxillectomy or, possibly, excision through an endoscopic approach. If inadequately excised, at least 25% to 35% will recur, usually within five years of treatment.

XIII. SQUAMOUS CELL CARCINOMA OF THE NASAL CAVITY

A. Introduction

Assessing the clinical and pathological features of primary squamous cell carcinoma of the nasal cavity is an exercise fraught with frustration because (i) the disease is uncommon and very few institutions have acquired a sufficiently large series for evaluation, (ii) the tumors are usually considered jointly with those occurring in the paranasal sinuses, (iii) many studies include a heterogeneous group of neoplasms and report end results as if only a single histological entity were involved, (iv) some investigators include or exclude tumors arising in certain regions of the nasal cavity, whereas others include all sites, (v) there is no uniformly acceptable system for staging of tumors to compare the efficacy of various therapeutic modalities, and (vi) survival rates are variously reported as actuarial, absolute, or disease free, further complicating evaluation (1–5).

With these limitations in mind, carcinomas of the nasal cavity and paranasal sinuses account for 0.2% to 0.8% of all malignancies and 3% of those occurring in the head and neck (6,7,8). When broken down according to site of origin, 58% to 60% of all sinonasal tumors

originate in the maxillary sinus, 24% to 30% in the nasal cavity and vestibule, 10% to 15% in the ethmoid sinus, and 1% in the sphenoid and frontal sinuses (9,10).

B. Etiology

Multiple risk factors have been associated with a wide variety of malignant tumors of the sinonasal tract. Among these are included (i) tobacco, (ii) ionizing irradiation (radium dial painters, thorium dioxide), (iii) occupational exposure to wood dust, nickel, and chromates (iv) boot and shoe manufacturing, (v) working in the textile industry, (vi) formaldehyde exposure, (vii) atmospheric pollutants, and (viii) history or presence of an IP or OSP (2,11,12).

Furuta et al. searched for the presence of HPV 16 and 18 in 49 squamous cell carcinomas of the sinonasal tract using polymerase chain reaction. The virus was detected in 14% of the tumors, raising the possibility that the virus might be etiologically related to some of the tumors (13). Interestingly, they observed that the presence of HPV was not related to local progression, occurrence of metastases, or the prognosis of the patients. Paulino et al. studied 15 non-Asian patients with squamous cell carcinoma of the anterior nasal cavity for the presence of EBV using immunohistochemistry and in situ hybridization. All tumors were negative for the virus, leading the investigators to conclude that squamous cell carcinoma in this site does not appear to be causally related to EBV (14).

C. Clinical Features

The incidence of squamous cell carcinoma of the sinonasal tract, adjusted for age and gender, is 0.3 to 1.0 case per 100,000 people per year in most countries (11). After the age of 35, the incidence rises steadily, reaching about five to seven cases per 100,000 people by age 80. It is practically nonexistent in children.

Squamous cell carcinomas of the nasal cavity is more common in males (52–97% of all cases) and occurs in individuals with a mean or median age of about 55 to 65 years (range 17–91 years) (Tables 13–15) (15–56). A nonhealing sore, “crusting” of the interior of the nose, epistaxis, rhinorrhea, and unilateral obstruction are common presenting symptoms. Local pain is a feature in only about one-fourth of patients (21,32).

On physical examination, the lesion presents as an ulcer or as a polypoid or sessile growth limited to one area of the nose, or it may completely fill the cavity. Others, particularly those of the vestibule, may manifest as an “infection,” with induration of the upper lip. Benign lesions, on the other hand, tend to be smooth, firm, localized, and mucosa covered (17).

There is no significant lateralization of carcinomas to either side of the nose (Table 16). Although 10% of tumors will present bilaterally, most of these are actually examples of unilateral disease that has perforated the nasal septum.

Table 13 Squamous Cell Carcinoma of the Nasal Vestibule: Clinical Features

References	No. of cases	Age (mean and/or median)	Males (%)	Local recurrence (%)	Positive regional nodes (%)	Distant metastasis (%)	Survival
Goepfert (22)	26	60	92	15	31	4	78% 5-yr absolute
Wang (24)	36	>50	61	26	16	10	74% NED at 3 yr
Johansen (34)	66	>50	74	35	19	5	77% 5-yr corrected
Schalekamp (35)	127	67	97	36	24	—	83% at 4-yr mean
Wong (36)	56	64	75	21	9	2	87% 5-yr specific
Barzan (44)	12	65	92	8	8	—	75% 5 yr
Poulsen (45)	29	>60	86	36	34	7	64% 5-yr actuarial
McCollough (46)	39	65	59	18	15	5	75% 5-yr absolute
Patel (43)	30	65	80	40	30	3	76% 5 yr
Mendenhall (50)	60	63	68	15	15	5	74% 5 yr
Horsmans (51)	66	68	52	24	8	2	85% 5-yr disease specific
Samaha (52)	14	67	64	36	21	—	—
Kummer (53)	47	—	81	9	13	4	—
Langendijk (54)	56	68	80	20	12	0	66% 5 yr
Mean	664	62	76	24	18	5	—

Abbreviation: NED, no evidence of disease.

Table 14 Squamous Cell Carcinoma of the Nasal Septum: Clinical Features

References	No. of cases	Age (Mean and/or Males median)	(%)	Local recurrence (%)	Positive regional nodes (%)	Distant metastasis (%)	Survival
Weimert (26)	14	56	71	21	7	14	80% at 5 yr
Beatty (32)	58	57	67	—	24	3	67% at 5 yr
LeLiever (33)	18	59	68	6	50	28	66% 5-yr absolute
DiLeo (55)	16	62	75	6	19	—	66% at 5 yr
Mean	106	59	70	11	25	15	—

Abbreviation: NED, no evidence of disease.

Table 15 Squamous Cell Carcinoma of the Nasal Cavity, all Sites: Clinical Features

References	No. of cases	Age (mean and/or median)	Males (%)	Local recurrence (%)	Positive regional nodes (%)	Distant metastasis (%)	Survival
Chung (30)	20	56	64	10	—	—	70% 3-yr actuarial
Shidnia (37)	21	65	52	29	29	10	64% 5-yr NED
Hawkins (39)	46	61	71	34	22	11	55% at 5 yr
Sakashita (48)	5	40	80	20	20	40	60% at 4.3 yr
Fornelli (56)	32	65	66	16	41	—	50% 5 yr
Mean	124	57	67	22	28	20	—

Abbreviation: NED, no evidence of disease.

Table 16 Lateralization of Cancer of the Nasal Cavity

References	No. of cases	Right N (%)	Left N (%)	Bilateral N (%)
MacComb (15)	60	25 (42)	31 (52)	4 (6)
Badib (21)	57	33 (58)	21 (37)	3 (5)
Bosch (25)	40	12 (30)	17 (43)	11 (28)
Lederman (57)	154	54 (35)	73 (47)	27 (18)
Robin (58)	129	67 (52)	62 (48)	—
Total	440	191 (43)	204 (46)	45 (10)

Less than 10% of patients (range 0–27%) will have positive regional lymph nodes at the time of diagnosis (22–24,29,34–36,41,43,45,46,48). Because it is a midline structure, nodal metastases may be ipsilateral, contralateral, or bilateral and typically involve the submandibular and submental and occasionally, the facial, preauricular, and parotid lymph nodes (10,22,24,31).

Although the interior of the nose can be divided into five areas—roof, septum, lateral wall, floor, and vestibule—squamous cell carcinoma of the nose is usually considered clinically under three categories: vestibule, septum, and nasal cavity proper (the remaining part of the nasal cavity). A discussion of squamous cell carcinoma at each of these sites follows.

Nasal Vestibule

The vestibule is the dilated cavity just inside the nose that is lined by skin and contains long hairs (vibrissae) (Fig. 38). It extends from the anterior opening of each nostril to the level of the limen nasi, a distinct ridge on the lateral nasal wall that corresponds to the superior margin of the greater alar cartilage and the zone of transition between the skin and the ciliated respiratory epithelium of the nasal mucosa. The lateral wall of the vestibule is formed by the lateral plate of the greater

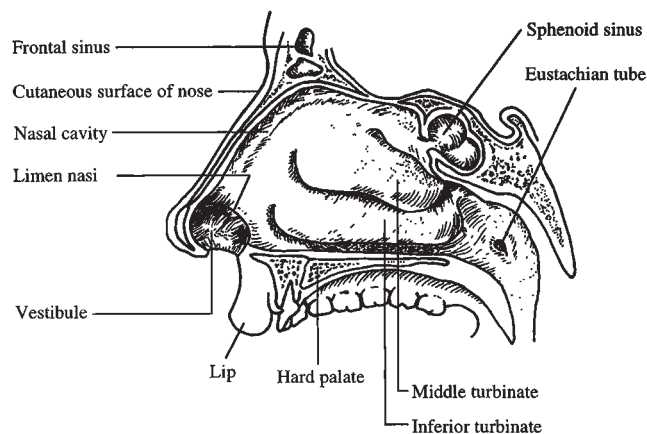


Figure 38 Diagram showing the internal anatomy of the nasal cavity and its relation to surrounding structures.

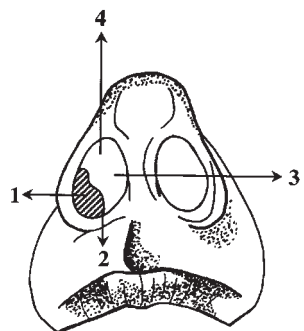


Figure 39 Diagram of inferior view of nose showing potential areas of growth of a vestibular carcinoma (*hatched area*): (1) laterally to invade the lateral alar cartilage or skin, (2) inferiorly to involve the upper lip or underlying bone, (3) medially to involve the septum, and (4) superiorly either along the septum or lateral nasal wall.

alar cartilage and the medial wall by the caudal nasal septum and columella. The intervening floor of the nose is also included as part of the vestibule.

Because the vestibule is lined by skin, some consider it as part of the integument, rather than the nasal cavity. Although vestibular tumors have a relation to skin cancers, they are more aggressive for the following reasons: (i) they frequently masquerade as an infectious process, which results in a delay in diagnosis; (ii) they often invade nearby important structures, such as the septum, cartilage, skin of the nose, upper lip, or underlying bone, which makes resection more difficult and imposes the need for cosmetic repair (Fig. 39); and (iii) the area is richly endowed with lymphatics, and lymph node metastasis, therefore, is not uncommon.

Although there is no uniform system for staging vestibular tumors, two have been proposed: the Wang

Table 17 Staging of Carcinoma of the Nasal Vestibule According to Wang

T1	The lesion is limited to the nasal vestibule, relatively superficial, involving one or more sites within.
T2	The lesion has extended from the nasal vestibule to adjacent structures, such as the upper nasal septum, upper lip, philtrum, skin of the nose or nasolabial fold, but not fixed to the underlying bone.
T3	The lesion has become massive, with extension to the hard palate, buccogingival sulcus, large portion of the upper lip, upper nasal septum, turbinate, or adjacent sinuses, fixed with deep muscle and bone involvement.

Source: From Ref. 24.

Table 18 Staging of Carcinoma of the Skin (Vestibule) According to the American Joint Committee

TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm, but not more than 5 cm, in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor invades deep extradermal structures (e.g., cartilage, skeletal muscle, or bone)

Source: From Ref. 52.

(Table 17) and the American Joint Committee on Cancer (AJCC) classifications (Table 18) (24,59). In a collective review of 222 vestibular carcinomas classified according to the Wang system, 60% were T1, 23% T2, and 17% T3 (24,34,35). Of 25 tumors staged by the AJC criteria, 52% were T1, 32% T2, none T3, and 16% T4 (45).

On average, 24% (range 8–40%) of patients with vestibular carcinomas will develop local recurrences following initial treatment, 18% (range 8–34%) will experience positive regional lymph nodes sometime during the course of their disease, and 5% (range 2–10%) will ultimately have distant metastases, usually to the lungs, liver, or bones (Table 13). Survival rates from various studies are also shown in Table 13.

Signs of poor prognosis include the following: (i) tumors larger than 1.5 cm; (ii) involvement of two or more sites in the vestibule; (iii) extension to the upper lip, columella, cartilage, or bone; (iv) local recurrence; and (v) positive regional lymph nodes, especially at the time of diagnosis (22,27,34,36,43).

Septum

Squamous cell carcinoma of the nasal septum most often arises from the anterior (70–75% of all cases) rather than posterior septum (26,32). In one series in which the size of the tumor was given, five were between 0 and 0.9 cm, eight were 1.0 to 1.9 cm, and nine were larger than 2 cm (33).

As the tumor enlarges, it may (i) ascend the septum to involve the roof of the nasal cavity, (ii) spread inferiorly along the septum toward the mucocutaneous junction, (iii) perforate the septum

and grow in the contralateral nasal cavity, or (iv) partially or totally fill the nasal cavity.

On average, 11% (range 6–21%) of patients with septal squamous cell carcinomas will experience local recurrences, 25% (range 7–50%) will develop positive regional lymph nodes during the course of their disease, and 15% (range 3–28%) will subsequently have distant metastasis (Table 14). Survival rates are also shown in Table 14. According to Beatty et al., there is no significant difference in the tendency to metastasize between anteriorly or posteriorly located tumors (32). Tumors larger than 2 cm and positive regional lymph nodes are signs of adverse prognosis (26,33).

Nasal Cavity

Squamous cell carcinoma of the nasal cavity arises most often from the lateral wall. From this site, the tumor may spread, if neglected, in several potential directions to involve the paranasal sinuses, orbit, cranial cavity, palate, or skin, and it may even invade cranial nerves (39).

On average, 22% (range 10–34%) of patients with squamous cell carcinomas of the nasal cavity will experience local recurrences, 28% (20–41%) will develop positive regional lymph nodes, and 20% (range 10–40%) will eventually have distant metastasis. Table 15 shows survival rates from various published series.

D. Pathology

Squamous cell carcinomas of the nose, regardless of the site of origin, are predominantly well to moderately differentiated. Poorly differentiated tumors are uncommon.

E. Treatment and Prognosis

Cancer of the nasal cavity can be treated by radiation, surgery, or both. Because of cosmetic concerns, many clinicians initially favor radiation, especially for vestibular tumors. The most common cause of death is uncontrolled tumor at the primary site. Because regional and distant metastases without local recurrence tend to be uncommon, adequate local control is tantamount to cure. Most local failures appear within one year of treatment and only rarely after two to three years (23,34–36,46,49). The majority are due to underestimating the extent of the disease or attempts by the surgeon or radiotherapist to be less radical to preserve function and avoid risks of complications.

Of all patients with carcinomas of the nasal cavity, 15% (range 6–28) either have or will develop a second primary malignancy (25,31,32). In the series of Bosch et al., 42% of these other tumors were discovered before, 16% at the same time, and 42% after appearance of the nasal lesion (25). Approximately, 40% of the second primaries are found in the head and neck, with two-thirds of these occurring in the larynx or pyriform sinus. The high incidence of

laryngeal carcinoma certainly raises the question of possible seeding from the nasal lesions (32). The remaining 60% of second primaries occur below the clavicles, usually in the lungs, gastrointestinal tract, or breasts.

XIV. SQUAMOUS CELL CARCINOMA OF MAXILLARY SINUS

A. Introduction

The maxillary sinuses are paired, usually symmetrical hollow cavities that lie in the body of each maxilla (Fig. 40). Each cavity is shaped similar to a pyramid, being based medially on the nasal cavity and projecting laterally to an apex in the zygoma (Fig. 41). Each sinus has a roof, a floor, and three walls—anterior, posterolateral, and medial (1). The base of the orbit forms the roof of the sinus, and the floor is formed by the alveolar process of the maxilla.

The anterior wall is the facial surface of the maxilla, whereas the posterolateral wall relates to the infratemporal and pterygopalatine fossa. The medial wall forms part of the lateral wall of the nasal cavity. Each sinus drains through an opening—the hiatus semilunaris—into the middle meatus of the lateral nasal wall.

Ohngren's line, a theoretical plane joining the medial canthus of the eye with the angle of the mandible, is sometimes used to divide the maxillary sinus into an anteroinferior portion (the infrastructure) and a superoposterior portion (the suprastructure) (2).

B. Clinical Features

Patients with squamous cell carcinoma of the maxillary sinus present late and die slowly. Fortunately, it is a relatively rare disease. It occurs more often in men (2–5 times) and affects individuals with a mean or median age of 60 to 65 years (3–21).

Signs and symptoms depend on the stage of the disease and direction of tumor growth. Early on they are vague and often confused with sinusitis. This

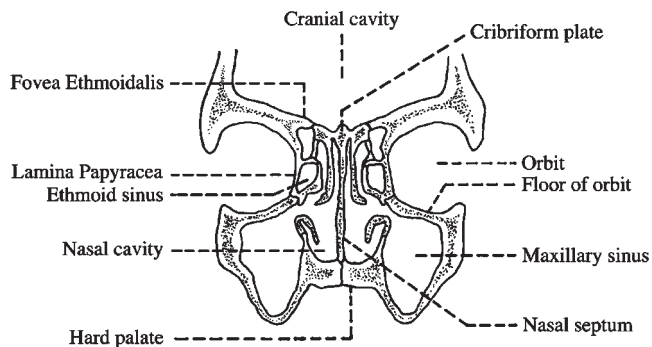


Figure 40 Coronal section through the maxillary sinuses showing relation of each sinus to other craniofacial structures.

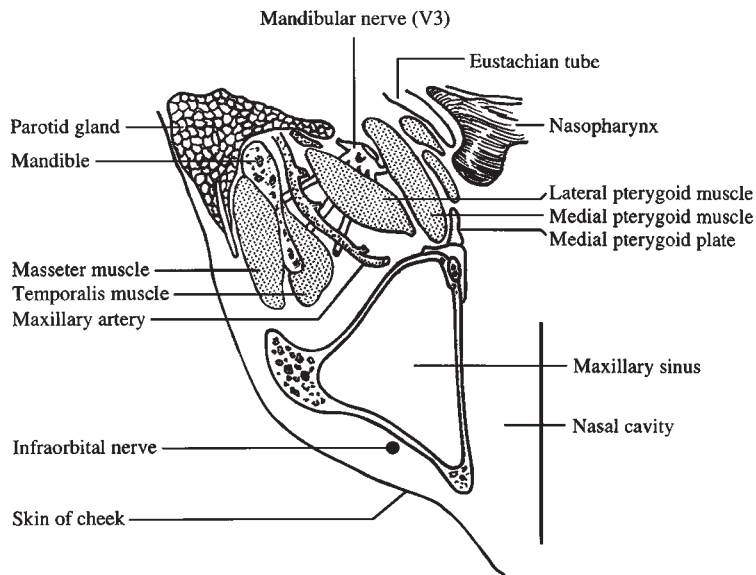


Figure 41 Cross-section through maxillary sinus showing anatomical relations.

Table 19 “T” Staging of Squamous Cell Carcinoma of the Maxillary Sinus

TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Tumor limited to the antral mucosa, with no erosion or destruction of bone
T2	Tumor with erosion or destruction of the infrastructure, including the hard palate or the middle nasal meatus
T3	Tumor invades any of the following: skin of cheek, posterior wall of maxillary sinus, floor of medial wall of orbit, anterior ethmoid sinus
T4	Tumor invades orbital contents or any of the following: cribriform plate, posterior ethmoid or sphenoid sinuses, nasopharynx, soft palate, pterygomaxillary or temporal fossae, or base of skull

Source: From Ref. 2.

results in an average delay of five to eight months before the diagnosis is established and is largely responsible for the 60% to 97% of patients who present with advanced T3 and T4 tumors (5,7,10–13,17,22–24) (Table 19).

Complaints can be grouped into five categories: nasal, oral, ocular, facial, and neurological. Nasal manifestations include unilateral stuffiness, obstruction, rhinorrhea, and epistaxis. Oral findings include pain referred to the upper premolar and molar teeth; loosening of the teeth; swelling or ulceration of the palate, alveolar ridge, or gingivobuccal sulcus; or a fistula. Common ocular features consist of swelling of the eyelids, excessive tearing, visual disturbances, and proptosis. Facial symptoms result from involvement of the anterior wall of the sinus and are characterized by swelling and asymmetry of the cheeks. Neurological manifestations are often due to tumor infiltration of the infraorbital branch of the fifth cranial nerve with subsequent numbness or paresthesia of the cheek.

Approximately 10% to 15% (range 4–21%) of patients will present with positive regional lymph nodes, usually the upper jugular, submandibular, and retropharyngeal (3,5,6,10,11,13,14,16–18,25). Distant metastases at the time of diagnosis, however, are uncommon (0–4%) (5,10,14,16,17,25).

There is no significant lateralization of tumors to either sinus (26,27). Bilateral primary squamous cell carcinomas of the maxillary sinuses, though described, are extremely rare and are predominantly metachronous, rather than synchronous (28–30). In a review of 351 patients with squamous carcinomas of the maxillary sinus, Shibuya et al. observed five patients (1.4%) who had bilateral carcinomas (28). In a similar study of 802 patients, Miyaguchi et al. noted that 10 (1.2%) had bilateral tumors (29). Of the five patients with bilateral carcinomas in the study of Shibuya et al., the interval between the diagnosis of the index and second primary tumor was more than five years in all patients (28). This is a unique experience, because most patients with squamous carcinomas of the maxillary sinus are usually dead of disease within five years and attest to the success that the Japanese have had in treating this deadly disease. Shibuya et al. also indicate that of those patients who survive more than five years, the incidence of bilateral cancers may even be as high as 5% (28).

C. Imaging

Computed tomography and MRI are indispensable, not only in determining the extent of disease but also in assisting the surgeon in selecting the best operative approach (31–34). Unfortunately, squamous cell carcinomas of the maxillary sinus are rarely diagnosed in an early stage. Most are advanced and, on imaging, show the sinus to be either partially or totally filled with a tumor, with destruction of one or more of the

bony walls. Extension into adjacent structures, such as the cheek, oral cavity, infratemporal fossa, and peri-orbital soft tissue, is not uncommon.

D. Pathology

The vast majority of squamous carcinomas are either well or moderately differentiated. Poorly differentiated tumors are uncommon.

E. Treatment and Prognosis

Because the tumors are generally advanced at the time of diagnosis, a combination of surgery and radiation is used in most instances, with or without chemotherapy (10,11,13,14,35–37). The Japanese, however, have had rather remarkable success, using primary irradiation followed by intra-arterial chemotherapy (5-fluorouracil and bleomycin), weekly cryosurgery, and immunotherapy (4,15,38,39).

One of the most difficult decisions in treating maxillary carcinoma is deciding whether or not the orbit should also be excised (40–44). This is a significant emotional burden for both the patient and surgeon and has resulted, in some instance, in the patient opting for less aggressive or even nonsurgical treatment. The surgical consensus on management of the orbit in cases of carcinoma approaching the orbital floor has changed from almost routine exenteration in the 1960s to a more current highly selective approach. Clinical evidence of invasion of the orbital fat or extraocular muscles, such as proptosis, diplopia, decreased visual acuity, and restricted ocular mobility are clear indications for orbital exenteration. Invasion of the bone of the orbital floor is currently not an absolute indication for removal. Stern et al., however, indicate that strong consideration should be given to orbital exenteration at the time of surgery when the orbital floor is resected, especially if postoperative radiation fields will include the eye (44). Otherwise, the preserved, radiated eye will almost assuredly be useless following radiation and may have to be removed at a later date.

Local recurrence, seen in about 30% to 45% (range 18–75%) of cases, is the most common cause of treatment failure and death (5,8,10,11,13,15–22,45). Virtually, all recurrences appear within two years of therapy and most within one year. During the course of the disease, 25% to 30% of patients will develop positive regional lymph nodes and 10% to 20% will experience distant metastases (3,5,6,8,10,11,16–22). Five-year survival rates, variously reported as actuarial, determinant, cumulative, crude, and not otherwise specified, average about 45% to 50% (range 22–72%) (4,11,13,16–24,40,45).

According to Weymuller et al. (46), patients who exhibit one or more of the following signs or symptoms have a greater than 75% chance of dying of their disease: facial numbness, facial swelling, diplopia, epiphora, denture pain, a mass in the palate or nasopharynx, proptosis, abnormal extraocular movement,

canine fossa or skin involvement, orbital edema, and positive cervical lymph nodes (46). Tumors that originate in the antral suprastructure and those that recur following initial curative therapy, regardless of the site of origin, are also associated with a poor prognosis.

XV. NONKERATINIZING CARCINOMA

A. Introduction

“Nonkeratinizing carcinoma” (NKC) is the official term sanctioned by the World Health Organization (WHO) for a distinctive variant of squamous cell carcinoma derived from respiratory (Schneiderian) mucosa and composed of mitotically active epithelial cells arranged in a characteristic ribbon-like pattern (1,2) (Fig. 42). Synonyms include cylindrical cell carcinoma, transitional cell carcinoma, Schneiderian carcinoma, respiratory epithelial carcinoma, and Ringertz carcinoma.

Although uncommon in our experience, it comprises in some series 10% to 20% of all sinonasal carcinomas (2–4).

B. Etiology

El-Mofty and Lu studied 39 carcinomas of the sinonasal tract [21 keratinizing squamous cell carcinoma, 8 NKCs and 10 sinonasal undifferentiated carcinomas (SNUCs)] for the presence of HPV, using the polymerase chain reaction (4). They observed that four of the eight NKCs (50%) contained HPV 16, 18, or 45, whereas only 19% of the keratinizing squamous carcinomas and 10% of the SNUCs were positive for the virus. Other than a possible link to HPV, its relationship to other risk factors such as smoking and atmospheric pollutants is unknown.

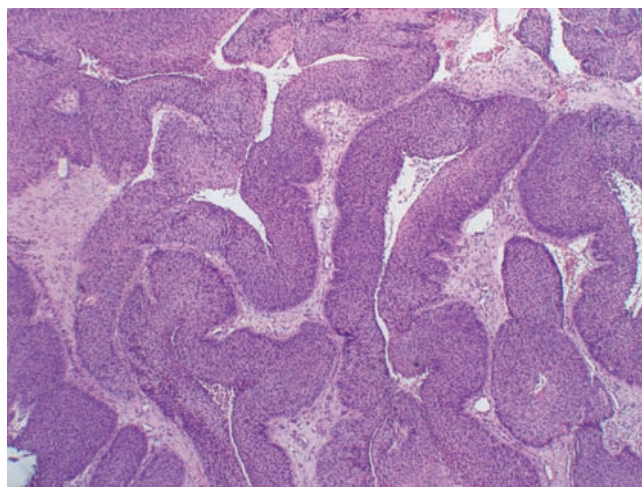


Figure 42 Nonkeratinizing carcinoma. Note the ribbons of tumor cells. At low magnification, the tumor is often mistaken for an inverted papilloma (H&E, 40×).

C. Clinical Features

NKCs have been described in patients from 23 to 92 years of age (average about 55–65 years) and exhibit a gender distribution of 1:1 to 1.6:1 in favor of males (2,4,5). Most arise in either the nasal cavity or maxillary sinus and manifest as nasal obstruction and epistaxis.

They are typically unilateral and, on examination, often appear polypoid masquerading as an ordinary sinonasal polyp or IP. Most are solitary, but in a review of 52 cases, Auerbach et al. observed that 12 (23%) of their patients had multifocal intranasal lesions (5).

D. Pathology

NKCs are frequently exophytic or polypoid with a smooth, corrugated papillary surface. Microscopically, they are composed of thick ribbons of multilayered nonkeratinized, mitotically active epithelial cells, which appear as invaginations of the surface epithelium (Fig. 42). Admixed mucous (goblet) cells and even rare foci of keratinization may be apparent. Elongated cells perpendicular to the basement membrane at times create a “cylindrical” appearance (Fig. 43).

NKCs tend to have a pushing margin, and many of the ribbons of cells are surrounded by intact basement membranes, thus appearing in situ. However, focal and sometimes diffuse invasion will often be apparent if enough tissue is available for examination.

Most NKCs develop *de novo*, but a few may arise from a concurrent IP. Exceptionally NKCs may contain foci of additional malignant tumors. Manivel et al. have described two cases of NKCs with

endodermal sinus tumor-like features (6). These “hybrid” NKCs tend to be more aggressive than the “pure” NKC; consequently, thorough microscopic examination of the excised tumor is essential.

E. Immunohistochemistry

NKCs are typically positive for CK 5/6, 8, 13, 14, and 19 and negative for CK 4, 7, and 10 (7). They also show strong and diffuse staining for p16, high labeling for Ki-67, and negative or weak reactivity for p53 (4,8).

F. Differential Diagnosis

At low magnification, NKC is very reminiscent of an IP, and, indeed, the two are often confused (Fig. 42). On higher magnification, however, the cells of an NKC, in contrast with those seen in IP, are more pleomorphic and mitotically active, with frequent loss of polarity (Fig. 43).

G. Treatment and Prognosis

Surgery, often supplemented with postoperative radiation, is the treatment of choice. Although NKC may metastasize to regional lymph nodes (10% of cases) or to more distant sites, it tends to be a locally aggressive tumor (2). It also seems to have a better prognosis than conventional squamous cell carcinoma.

XVI. SINONASAL UNDIFFERENTIATED CARCINOMA

A. Introduction

SNUC was originally described by Frierson et al. in 1986 and was defined as a high-grade malignant epithelial neoplasm of the nasal cavity and paranasal sinuses of uncertain histogenesis with or without neuroendocrine differentiation but without evidence of squamous or glandular differentiation (1). More recently, the WHO has defined it as “a highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis that typically presents with locally extensive disease. It is composed of pleomorphic tumour cells with frequent necrosis, and should be differentiated from lymphoepithelial carcinoma and olfactory neuroblastoma” (2).

Although the histogenesis of SNUC is uncertain, the presence of dysplasia or in situ carcinoma of the overlying mucosa observed in a few tumors suggests that it is derived from the Schneiderian membrane and therefore is of ectodermal origin. Limited neuroendocrine differentiation as seen by immunohistochemistry and electron microscopy has led some to speculate that SNUC may be a neuroendocrine neoplasm related to large cell neuroendocrine carcinoma as seen in the lung (3). More recently, Ejaz and Wenig have proposed that the definition of SNUC should be expanded to include those tumors that show limited squamous differentiation (4).

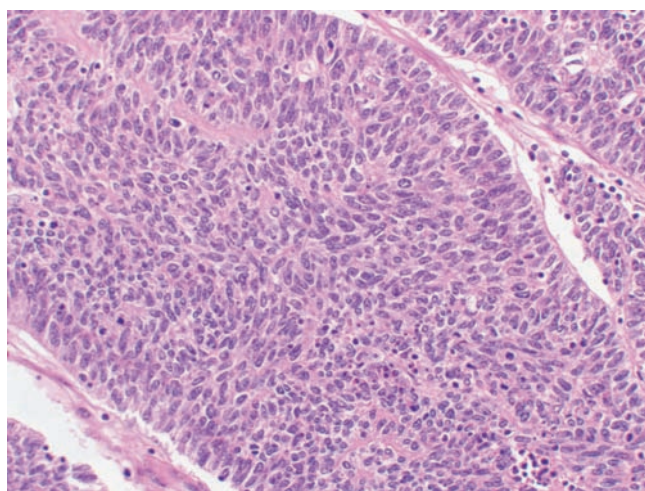


Figure 43 Nonkeratinizing carcinoma. The cells are mitotically active with loss of polarity. Note the absence of keratinization. The cells along the basement membrane are elongated or cylindrical, hence the synonym “cylindrical cell carcinoma” (H&E, 200×).

B. Etiology

Many of the patients with SNUC either are or have been smokers. Whether or not there is a relation between this habit and the development of the tumor is unknown. Thus far, no specific occupational exposure has been incriminated (1).

Lopategui et al. and Gallo et al. studied a combined series of 35 SNUCs for the presence of the EBV, using in situ hybridization, and found evidence of the virus in 12 cases (34%) (5,6). The virus was found only in those patients of Asian or Italian descent. None was found in those patients tested from the United States. At least some of their EBV-positive tumors on critical review are, no doubt, examples of unrecognized primary lymphoepitheliomas of the sinonasal tract (7). More recently, Cerilli et al., using strict criteria, studied 25 additional SNUCs for the presence of EBV, using in situ hybridization. All of their patients were from the USA, and all were negative for the virus (8). It would thus appear that SNUC has little, if any, relationship to EBV.

A few cases have also been observed in patients who have a history of previous nasopharyngeal carcinoma (NPC) treated with irradiation (7).

Another two cases of SNUC have been described in patients with a past history of retinoblastoma (9,10). Whether mutations of the retinoblastoma gene are responsible for some cases of SNUC is also in need of further studies.

C. Clinical Features

SNUC is a rare, highly aggressive malignant tumor of the nasal cavity and paranasal sinuses. In a collective review of 116 cases, the male to female ratio was 3:1 with a mean age at diagnosis of about 55 to 58 years (range 20–84 years) (7,8,11–14). It most often originates in the nasal cavity, but at the time of presentation the tumor is often found unexpectedly to be quite extensive, involving not only the nasal cavity and one or more of the paranasal sinuses but also the orbit and cranial cavity.

As such, patients typically present with multiple signs and symptoms of about three- to four-months duration. Among these are included nasal obstruction, epistaxis, facial pain, headaches, proptosis, visual disturbances, cranial nerve palsies, impaired mental function, neck mass, and weight loss. Tumors localized to the nasal cavity or a single sinus are uncommon.

D. Pathology

Microscopically, the tumors are composed of small to medium-sized polygonal cells that grow in sheets, nests, wide trabeculae, and/or ribbons (Figs. 44 and 45). The nuclei are round to oval, hyperchromatic, and mild to moderately pleomorphic, but on occasions, may be vesicular. Nucleoli vary from inconspicuous to large. The cells tend to have mild to moderate amounts of eosinophilic to amphophilic cytoplasm. Mitoses are numerous [10–50 or more per 10 high-power fields

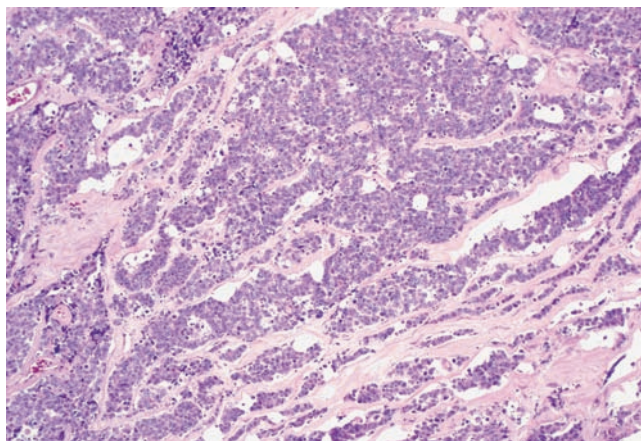


Figure 44 Sinonasal undifferentiated carcinoma growing as sheets and trabeculae of cells (H&E, 100×).

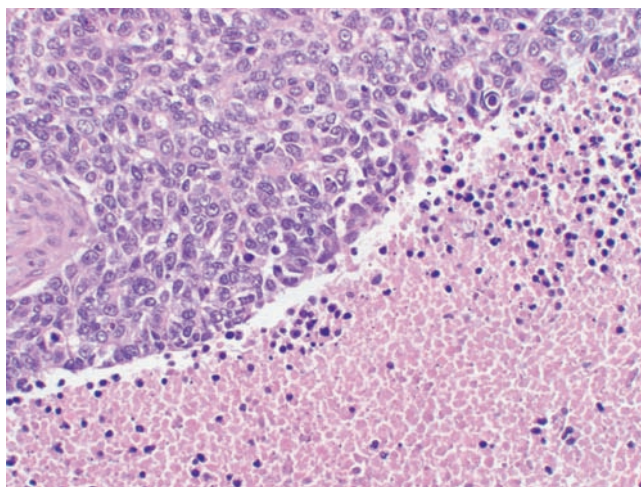


Figure 45 Higher magnification of the sinonasal undifferentiated carcinoma shown in Fig. 44 showing a sheet of cells associated with extensive necrosis. Mitoses are usually prominent (H&E, 200×).

(HPFs)] and angiolymphatic invasion and necrosis are prominent.

Infrequently, one may see changes of dysplasia or carcinoma in situ of the overlying mucosa (Fig. 46). Strictly defined, squamous and glandular differentiation should not be seen nor rosettes or a neurofibrillary stroma (see discussion in the sect. "Introduction").

E. Immunohistochemistry

The immunoprofile varies from case to case. The tumors are, however, consistently positive for epithelial markers, including parakeratin and the simple CK 7,8, and 19 (4,7,8,15,16). They are negative for CK4,

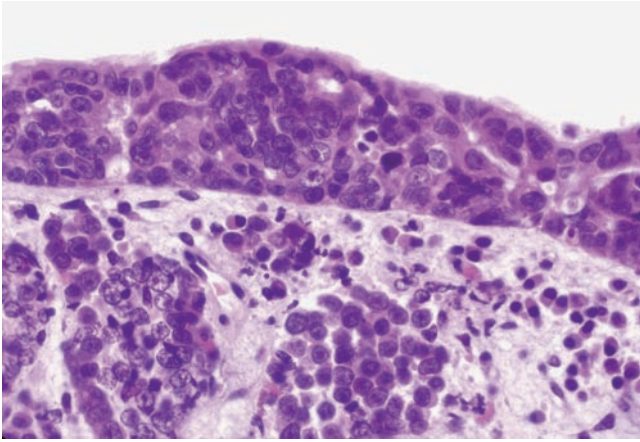


Figure 46 Sinonasal undifferentiated carcinoma. Note the surface component of in situ carcinoma and compare with similar cells invading the lamina propria (H&E, 400 $\times$).

5/6, and 14. Variable reactivity has been observed with p63. Less than half the cases are reported to be positive for epithelial membrane antigen, neuron-specific enolase, and p53 (8). The cells rarely decorate for synaptophysin, chromogranin, and Leu-7 and then only in a spotty or patchy distribution. A few cases have also been positive for CD-99, but in these instances, the staining is cytoplasmic rather than membranous as characteristically seen in peripheral neuroectodermal tumor/Ewing's sarcoma (8).

F. Electron Microscopy

Ultrastructurally, the cell membranes are smooth to moderately ruffled and exhibit small desmosomes and poorly formed junctional complexes (1). Nuclear membranes are smooth to mildly irregular. The cytoplasm contains small amounts of rough endoplasmic reticulum, polyribosomes, and mitochondria. Golgi complexes are usually prominent, and lysosomes and lipid droplets may be found; however, bundles of tonofilaments are absent. A few neurosecretory granules have been observed in rare cells, but only after a prolonged search (1).

G. Differential Diagnosis

The differential diagnosis includes a myriad of round cell tumors that can occur in the sinonasal tract (16,17). Among the more common ones are olfactory neuroblastoma (ONB), NPC, malignant lymphoma, malignant melanoma (MM), rhabdomyosarcoma, small cell neuroendocrine carcinoma (SCNEC), and peripheral neuroectodermal tumor/Ewing's sarcoma. Immunohistochemical stains that are useful in separating these tumors are shown in Tables 20 and 21.

The three tumors that are most often confused with SNUC are the ONB, NPC (undifferentiated type), and SCNEC. In addition to their different immunohistochemical profiles, ONB does not exhibit the degree of necrosis, mitotic activity, nuclear pleomorphism, or tendency for angiolymphatic invasion as seen in SNUC. Features that are useful in separating these three tumors are shown in Tables 22, 23, and 24.

Table 20 Immunohistochemical Staining of Selected Round Cell Tumors of the Sinonasal Tract

Tumor	CK	EMA	LCA	Synaptophysin	HMB-45	Desmin	Vimentin	CD99
SNUC	+	+/-	-	-/+	-	-	-	-/+
ONB	- ^a	-	-	+	-	-	-	-
NPC	+	+	-	-	-	-	-	-
Lymphoma	-	-	+	-	-	-	+	-/+
Melanoma	-	-	-	-	+	-	+	-
Rhabdomyosarcoma	-	-	-	-	-	+	+	-/+
SCNEC	+	+	-	+/-	-	-	-	-
PNET/ES	-/+	-	-	-/+	-	-	+	+

^aONB is typically negative for CK, but may infrequently focally express low-molecular weight CK.

Abbreviations: CK, cytokeratin; EMA, epithelial membrane antigen; LCA, leukocyte common antigen; SNUC, sinonasal undifferentiated carcinoma; ONB, olfactory neuroblastoma; NPC, nasopharyngeal carcinoma; SCNEC, small cell neuroendocrine carcinoma; PNET/ES, peripheral neuroectodermal tumor/Ewing's sarcoma.

Table 21 Cytokeratin Expression in Sinonasal Tumors

Tumor	4	5/6	7	8	10	13	14	19
SCC (N = 10)	30%	90%	60%	90%	—	90%	80%	90%
NKSCC (N = 10)	—	90%	—	90%	—	80%	80%	90%
UNPC (N = 5)	—	80%	—	80%	—	80%	—	100%
SNUC (N = 6)	—	—	50%	100%	—	—	—	50%

Abbreviations: SCC, squamous cell carcinoma; NKSCC, nonkeratinizing squamous cell carcinoma; UNPC, undifferentiated nasopharyngeal carcinoma; SNUC, sinonasal undifferentiated carcinoma.

Source: From Ref. 15.

Table 22 ONB Vs. SNUC

Feature	SNUC	ONB
Age (average)	55–58	40–45
Site	Multiple sites	Roof of nasal cavity
Prognosis	45% 2 yr	60–80% 5 yr
Ocular-cranial nerve involvement	Common	Uncommon
Anaplasia	Common	Uncommon
Mitoses	Numerous	Variable
Necrosis	Prominent	Uncommon
Vascular invasion	Prominent	Uncommon
Neurofibrillary stroma	Absent	Common
HW rosettes	Absent	Common
Keratin	Most	Focal at most
EMA	Occasional	0%
NSE	Occasional	100%
S-100	Rare	Sustentacular
Synaptophysin	Rare	100%
Neurosecretory granules	Rare	Numerous

Abbreviations: SNUC, sinonasal undifferentiated carcinoma; ONB, olfactory neuroblastoma; HW, Homer Wright; EMA, epithelial membrane antigen; NSE, Neuron-specific enolase.

Table 23 SNUC Vs. UNPC

Feature	SNUC	UNPC
Location	Sinonasal tract	Nasopharynx
Clinical	Large primary, +/- cervical lymph nodes	Small primary, +cervical lymph nodes
Imaging	Marked destruction and spread beyond site of origin	Little destruction or spread beyond site of origin
Growth	Trabeculae, nests, sheets	Syncytial
Cells	Hyperchromatic to vesicular nuclei with or without nucleoli	Large, vesicular nuclei with prominent nucleoli
Mitoses	Very prominent	Not prominent
Necrosis	Very prominent	Not prominent
Vascular invasion	Very prominent	Not prominent
Lymphocytes	Absent to mild	Heavy infiltrate
Epstein-Barr virus (United States)	–	+

Abbreviations: SNUC, sinonasal undifferentiated carcinoma; UNPC, undifferentiated nasopharyngeal carcinoma.

Table 24 SNUC Vs. SCNEC

Feature	SNUC	SCNEC
Spindle cells	–	+
Nucleoli	+/-	–
Nuclear molding	–	+
DNA coating	–	+
Dysplasia—CIS	+/-	–
Synaptophysin	–	+/-
Thyroid transcription factor	–	+/-
Dot-like keratin positivity	–	+/-

Abbreviations: SNUC, sinonasal undifferentiated carcinoma; SCNEC, small cell neuroendocrine carcinoma; CIS, carcinoma in situ.

H. Treatment and Prognosis

SNUC is a very lethal neoplasm. Although a few individuals have survived for more than five years, the two-year survival rate is about 45% (range 10 months median survival to 63% at 5 years) (7,8,11–14). Most patients die of local disease, but cervical lymph node (15–50% of cases) and distant metastases (20–45% of cases), primarily to lungs, liver and bones, do occur (7,8,11,13).

Current therapy consists of chemotherapy, radiation, and surgery (18,19). Contradictions to surgery include bilateral orbital involvement, optic nerve or optic chiasm extension, frank brain invasion, prevertebral fascia involvement, distant metastasis at presentation, and poor medical condition (20).

XVII. NEUROENDOCRINE CARCINOMA

The term “neuroendocrine carcinoma (NEC)” without further qualification should not be used as a specific diagnosis because it is not only confusing but is also meaningless. Some, for instance, have used it to describe typical carcinoids (well-differentiated NEC), atypical carcinoids (moderately differentiated NEC), and SCNECs (poorly differentiated NEC) (1–5). Silva et al. and Ordonez and Mackay have also described a group of tumors of the nasal cavity that they, unfortunately, have referred to as simply “neuroendocrine carcinomas” (6,7). Whether their tumors are actually small cell carcinomas, as claimed by some (8); represent a spectrum of ONBs, as suggested by others (7,9); or represent a new entity is uncertain.

Noteworthy is that the most recent edition of the WHO’s book on head and neck tumors does not recognize NEC as a specific lesion (10). Because a variety of neuroendocrine tumors (ONB, invasive pituitary adenoma, and others) may involve the nasal cavity and paranasal sinuses, we strongly recommend that the classification and terminology proposed by the WHO be used to avoid any future confusion. If a neuroendocrine tumor does not conform to the WHO classification, then the term “neuroendocrine carcinoma, not otherwise specified type” might be appropriate, and certainly less confusing. The tumor can then be graded as well, moderately, or poorly differentiated.

XVIII. SMALL CELL NEUROENDOCRINE CARCINOMA

A. Introduction

Small cell neuroendocrine carcinoma (SCNEC, small cell carcinoma, oat cell carcinoma, small cell undifferentiated carcinoma) similar to those seen in the lung is now being recognized with increased frequency in a variety of extrapulmonary sites. In the head and neck, the two most common sites are the larynx and salivary glands (1–3).

They are distinctively uncommon in the sinonasal tract, and in this location, lack of uniform terminology and confusion with other “round or

undifferentiated" tumors preclude an accurate assessment of their behavior. For instance, cases 3 (with multinucleated giant cells) and 4 (with prominent nucleoli) reported by Kameya et al. do not conform to our concept of SCNEC (4). Whether the "neuroendocrine carcinomas," described by Silva et al. and Ordonez and Mackay, are examples of SCNECs or some other entity is uncertain, and, accordingly, they too are not considered (5,6). For this discussion, we have accepted 48 cases in the literature as possible examples of SCNEC of the sinonasal tract (2,4,7–16).

B. Clinical Features

SCNEC of the sinonasal tract has been described in patients from 16 to 79 years of age, with an average of about 50 to 55 years, and a gender distribution of 1:1 to 1.5:1 in favor of males.

It originates either within the nasal cavity or the paranasal sinuses, especially the ethmoid and maxillary, and may remain localized to these sites, or it may spread to the orbit, cribriform plate, or cranial cavity. Symptoms, therefore, depend on the extent of disease and include intermittent epistaxis, nasal obstruction, progressive swelling and deformity, proptosis, visual disturbances, cranial nerve palsy, and pain.

A few SCNECs have also been associated with paraneoplastic endocrine syndromes of ectopic adrenocorticotrophic hormone production and in appropriate secretion of antidiuretic hormone (4,13,17). One tumor was found to contain a high content of calcitonin on chemical examination, but was not associated with hormonal symptoms (4). The occurrence of a paraneoplastic syndrome is an ominous feature with death ensuing within six months of onset.

C. Imaging

Imaging studies may show only a soft-tissue mass limited to the sinonasal tract, with or without obstructive opacification of the adjacent sinuses. Other tumors exhibit considerable osteodestruction, with invasion of the orbit, cribriform plate, or cranial cavity.

D. Pathology

SCNECs of the sinonasal tract presumably arise from mucoserous glands or from an uncommitted (stem) cell of the surface epithelium (2). Microscopically, they are identical with their pulmonary counterpart and, as such, are composed of short, spindle cells, with sparse, poorly defined cytoplasm, and hyperchromatic nuclei without nucleoli (Fig. 47). Nuclear molding, frequent mitoses, and necrosis are common.

Tumors composed of slightly larger cells, with round, hyperchromatic nuclei, and more abundant cytoplasm have also been described (12). These are similar to the "intermediate" type of SCNEC seen in the lung. A few may exhibit divergent differentiation, with foci of obvious squamous cell carcinoma or adenocarcinoma.

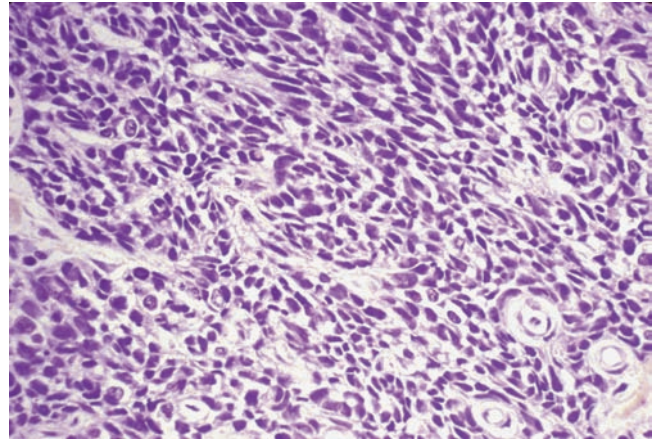


Figure 47 Small cell neuroendocrine carcinoma. Similar to their counterpart in the lung, the small cells have poorly defined cytoplasm and dense, hyperchromatic, round to short spindled nuclei devoid of nucleoli (H&E, 400×).

SCNECs characteristically grow in the lamina propria as sheets or small clusters of cells beneath an intact or ulcerated epithelial surface. If the latter is intact, it typically shows no significant dysplasia. In some instances, the tumor is intimately associated with mucoserous glands, often appearing to arise from them.

E. Immunohistochemistry

The tumors are positive for AE1/3 and CAM5.2, occasionally in a dot-like pattern. They are also usually positive for neuron-specific enolase, chromogranin, and synaptophysin and negative for S-100 protein (14). Only about 40% of extrapulmonary SCNECs, however, express thyroid transcription factor-1 (18). At least one tumor has been reactive for 0-13. By in situ hybridization, all tumors have been negative for the EBV (14).

F. Electron Microscopy

Neurosecretory granules may or may not be seen. Cell junctions are present to a variable degree, ranging from absent to well-formed desmosomes. Occasionally, bundles of tonofilaments are observed (19).

G. Differential Diagnosis

The differential diagnosis includes ONB, SNUC, basaloid squamous cell carcinoma (BSCC), and metastatic pulmonary SCNEC.

ONB is characteristically a low-grade neoplasm and does not show the prominent necrosis, mitotic activity, or nuclear pleomorphism of SCNEC. It is also composed of "round" rather than short spindle cells and frequently exhibits rosettes (Homer Wright, Flexner–Wintersteiner) and a neurofibrillary matrix.

Moreover, in contrast to SCNEC, which is diffusely positive for CK and often positive for thyroid transcription factor-1, ONB is usually negative for both.

Features that separate SCNEC from SNUC are shown in Table 24. BSCC is negative for chromogranin and synaptophysin and, if the biopsy is large enough, will exhibit areas of squamous differentiation. Although the sinonasal tract is an uncommon site of metastasis for pulmonary SCNEC, an origin from the lung should always be excluded by appropriate imaging and cytological studies.

H. Treatment and Prognosis

Despite multimodality therapy, SCNEC of the sinonasal tract is an aggressive neoplasm with a poor prognosis. Approximately, 35% to 45% of patients will experience local recurrence, 20% to 45% positive cervical lymph nodes, and 20% to 75% distant metastases, usually to the lungs, liver, bones, and brain (14–17,20,21). The median survival is about two to three years, with a five-year survival of 29% (15,16).

XIX. LYMPHOEPITHELIAL CARCINOMA

A. Introduction

Lymphoepithelial carcinoma (LEC) is a rare, newly recognized tumor of the nasal cavity and paranasal sinuses that is often mistaken for SNUC (1–7). Other than location (sinonasal tract vs. nasopharynx), it is otherwise histologically similar to the undifferentiated variant of nasopharyngeal carcinoma.

Additional terms that have been applied to this tumor include nasopharyngeal-type undifferentiated carcinoma, undifferentiated carcinoma with lymphoid stroma, undifferentiated carcinoma, and lymphoepithelioma-like carcinoma.

B. Etiology

Regardless of geographic location and ethnicity, almost all sinonasal LECs have been associated with the EBV (1,4,6).

C. Clinical Features

The tumor is two to three times more common in males and, thus far, has occurred only in adults of 31 to 75 years of age (mean about 45–55 years) (1,4,6).

Patients typically present with nasal obstruction, blood-tinged rhinorrhea, or epistaxis. Orbital or intracranial extension may also result in visual disturbances, proptosis, or cranial nerve dysfunction.

D. Imaging

The tumor originates most often in the nasal cavity and only infrequently in the sinuses. If neglected, it may involve one or more of the sinuses or invade the orbit or cranial cavity. Imaging is especially important

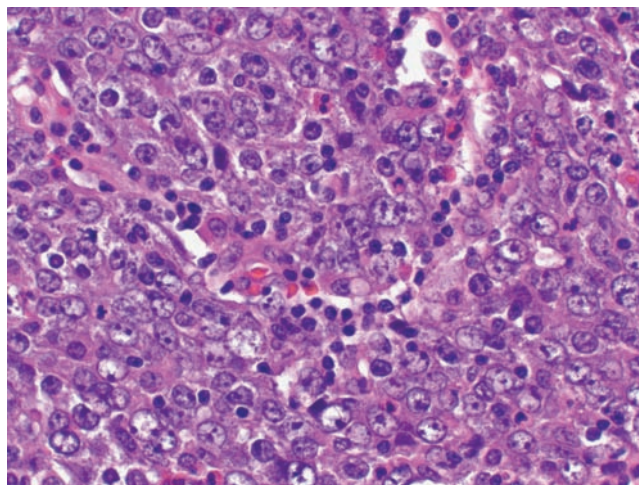


Figure 48 Lymphoepithelial carcinoma composed of cells with poorly defined cytoplasm, large round nuclei, and prominent nucleoli. Note the admixed lymphocytes. Compare with Fig. 68 (H&E, 400 $\times$).

to exclude local-regional spread from a primary nasopharyngeal carcinoma.

E. Pathology

LEC grows as large syncytial masses, small aggregates, and/or individual cells without a desmoplastic response. Individual cells have eosinophilic to amphophilic cytoplasm and large round nuclei with prominent nucleoli (Fig. 48). An intraepithelial component is observed in some instances as well as foci in which the tumor cells assume a spindled morphology. Mitoses and necrosis are infrequent to absent, and keratinization is not evident. Although lymphocytes and plasma cells permeate the tumor, a few cases have been observed that are relatively devoid of these cells (6).

F. Immunohistochemistry

LEC is positive for pankeratin and epithelial membrane antigen and negative for leukocyte common antigen, neuron-specific enolase, synaptophysin, and chromogranin. According to Franchi et al., they are also positive for CK 5/6, 8, 13, and 19 and negative for CK 4, 7, 10, and 14 (5) (Table 21).

G. Differential Diagnosis

The tumor is most often mistaken for SNUC and a primary NPC.

SNUC, in contrast to LEC, exhibits extensive necrosis, mitoses, and angiolymphatic invasion and is almost always negative for the EBV. SNUC is also usually negative for CK 5/6 and 13 (5). LEC, on the other hand, is positive for the EBV and also usually positive for CK 5/6 and 13 (Table 21).

Primary NPC can only be excluded by demonstrating the absence of tumor in the nasopharynx.

H. Treatment and Prognosis

Effective therapy of LEC of the sinonasal tract is still evolving, but like its counterpart in the nasopharynx, irradiation appears to be the mainstay. In a review of 13 cases, Jeng et al. observed a 61% disease-free survival at a median follow-up of 48 months (6). Three (23%) of their patients had positive cervical lymph nodes and one (8%) distant metastasis (bone).

XX. INTESTINAL-TYPE ADENOCARCINOMA

A. Introduction

Adenocarcinomas comprise 10% to 20% of all malignant tumors of the nasal cavity and paranasal sinuses and can be divided into four types (Table 25) (1–3). The intestinal-type adenocarcinoma (ITAC) bears a close resemblance to adenocarcinoma of the colon and, in some instances, even to villous adenoma (4,5). A few may even resemble normal small intestinal mucosa (6).

In the past, ITAC has been referred to as “colonic-type adenocarcinoma, mucinous adenocarcinoma, heterotopic tumor with intestinal mucous membrane, enteric-type adenocarcinoma, or nonspecific adenocarcinoma” (7–10). Because they may have features in common with either the large or small intestine and because the term “enteric” is sometimes used as a synonym for the small intestine (e.g., enteritis vs. colitis), the term “intestinal-type adenocarcinoma” has been proposed and adopted by the WHO (11,12).

B. Etiology

Interest in the ITAC peaked in the 1960s when Hadfield, a British otolaryngologist, astutely observed an increased incidence of this tumor among woodworkers employed in the furniture industry of Oxfordshire and Buckinghamshire, United Kingdom. Her observation was initially reported by her colleague, Macbeth, in 1965 and subsequently by Acheson, Cowdell, Hadfield, and Macbeth in 1968 (13,14). It has since become apparent that the risk for developing ITAC is not limited to England, but also occurs in the wood industries of many countries (15–27).

In a review of 5785 patients with sinonasal malignancies from 17 countries, Mohtashamipour et al. observed that 23% were woodworkers, and of these, 64% had adenocarcinomas (24). The risk for developing ITAC in the furniture worker exposed to

wood dust is 70 to 500 times that of the nonwoodworker (28,29). Dust particles measuring 5 μ m or more and primarily from the hardwood trees, beech, oak, and mahogany are thought to be responsible for the disease, rather than the lacquers, varnishes, and adhesives applied to the furniture. The inhaled particles are concentrated in the anterior part of the nasal septum and the anterior end of the middle turbinate, where they induce cuboidal or squamous metaplasia with impairment of the mucociliary clearance mechanism (30,31). This results in prolonged mucosal contact of the carcinogen present within the dust. The potential chemical or physical carcinogen (i.e., wood dust and its natural products or wood dust with both natural products and chemical additives) has not been adequately defined (26).

The average interval from first dust exposure to the appearance of the carcinoma is 40 years (range 7–69 years) (24). In one of Hadfield’s patients, the length of exposure to wood dust was only 18 months (30). In other studies, the length of dust exposure has ranged from 5 to 55 years (26). The risk for ITAC does not appear to decrease until at least 15 years after termination of occupational exposure to wood dust (26).

Although the majority of tumors associated with wood dust exposure are adenocarcinomas, there is also an increased incidence of squamous cell carcinomas, especially among woodworkers in Japan (21). Interestingly, in contrast with ITACs, which are associated with hard wood exposure, squamous cell carcinomas are more common in those exposed to soft woods (pine and spruce) (26).

There is also an increase in nasal cancers among individuals exposed to leather dust, especially in the shoe industry, and possibly to flour in the baking profession (17,28). However, in these occupations, the tumors are evenly distributed between ITAC and squamous carcinomas. Not all ITACs, however, are related to an occupational exposure. They may occur sporadically (11).

It has also been suggested that patients with an occupational exposure to wood dust may be at risk for developing other site-specific malignancies. Among these are Hodgkin’s disease and carcinomas of the skin, gastrointestinal tract, and lungs (26). More studies, however, are needed to substantiate these alleged associations.

C. Clinical Features

ITACs can be divided clinically into two categories: those related to occupational exposure (O-ITAC), and those that occur sporadically (S-ITAC) without a known history of occupational exposure. There are differences between the two. O-ITAC arises primarily in the nasal cavity and ethmoid sinus region, and 85% to 95% of patients are men (11). The male predominance is probably related to the fact that very few women are employed as woodworkers. S-ITAC, on the other hand, may also occur in the same site(s) as the O-ITAC, but these tumors are relatively more common in the maxillary sinus. In addition, S-ITACs occur equally between the two sexes. The average age

Table 25 Classification of Adenocarcinomas of the Nasal Cavity and Paranasal Sinuses

Salivary type
Intestinal type
Nonintestinal type (seromucinous)
Metastatic

at diagnosis for both types is about 58 years (range 12–86 years) (11).

Although most ITACs occur in the sinonasal tract, they are not unique to this site. Spiro et al. have described three arising in the oral cavity: one in the palate, one in the floor of the mouth, and one in the cheek-lip area (32). Lopez and Perez have also reported another case in the pharynx (33). Some of the rare mucinous adenocarcinomas of the major salivary glands described by Ellis and Aclair may be additional examples (34).

The most common presenting symptom is unilateral nasal obstruction, followed by epistaxis and purulent or clear rhinorrhea (4,7,11,25,35–39). Larger, more extensive tumors result in facial pain, mass of the cheek, proptosis, and visual or neurological symptoms. Cervical lymph node and distant metastases are rarely present at the time of initial presentation.

On physical examination, the tumors are polypoid, papillary, or nodular and dark red, gray-white, or pink-gray. Most are friable. Some are ulcerated and hemorrhagic, whereas others are mucoid.

Barnes has described one patient with an advanced tumor of the maxillary sinus that was associated with pretreatment borderline abnormal serum level of carcinoembryonic antigen (11). Whether this laboratory test has any role in monitoring the course of the disease is uncertain.

D. Imaging

Imaging studies are essential in determining the extent of disease and the operative approach. Early lesions show only a soft-tissue mass with little, if any, evidence of bone destruction. Other tumors are associated with considerable osteodestruction and invasion of contiguous structures, such as the orbit and cranial cavity. A few may even involve the contralateral sinonasal tract.

As the tumor enlarges, it interferes with drainage of nearby sinuses. The ensuing obstructive sinusitis then may interfere with optimal preoperative evaluation and staging.

E. Pathology

There are two generally accepted histological classifications of ITAC. Barnes, in 1986, proposed that they be divided into five types: papillary, colonic, solid, mucinous, and mixed (11). Kleinsasser and Schroeder, in 1988, suggested four categories: papillary tubular cylinder cell, alveolar goblet cell, signet ring cell, and transitional (19). They further divided their papillary-tubular cylinder cell variant into three additional subtypes: I (well differentiated), II (moderately differentiated), and III (poorly differentiated). These two classifications actually share many similarities, and their use depends on personal preference. Table 26 shows their interrelations.

The papillary-type (papillary-tubular cylinder cell-I) is characterized by highly branched fibrovascular fronds and glands (tubules) covered or lined by tall

Table 26 Classification and Survival of Intestinal-Type Adenocarcinoma

Barnes (11)	Kleinsasser and Schroeder (19)	3-yr cumulative survival ^a
Papillary	PTCC-I	82%
Colonic	PTCC-II	54%
Solid	PTCC-III	36%
Mucinous	Alveolar goblet	48%
	Signet ring	0%
Mixed	Transitional	71%

^aSurvival data derived from Ref.19.

Abbreviation: PTCC, papillary tubular cylinder cell.

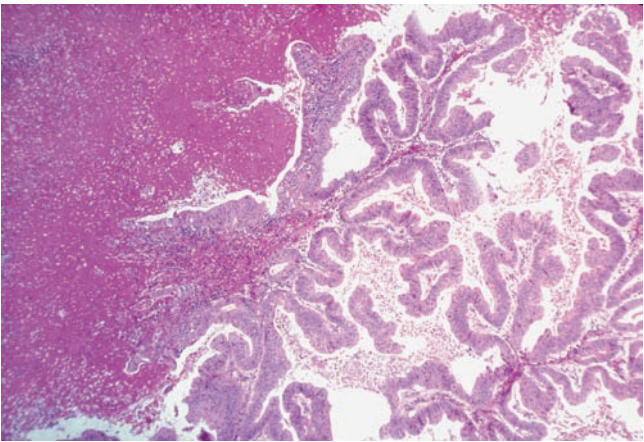


Figure 49 Papillary variant of intestinal-type adenocarcinoma. Note the highly branched papillae with thin fibrovascular cores (H&E, 40×).

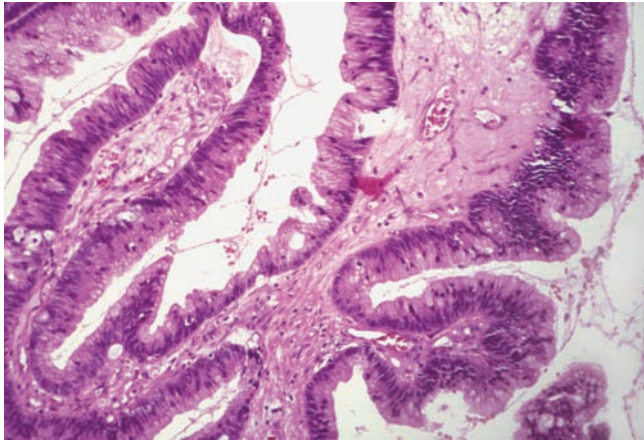


Figure 50 High magnification of a grade I (well differentiated) papillary variant of intestinal-type adenocarcinoma. Note the uniform, basally located nuclei (H&E, 200×).

nonciliated, columnar (cylinder) cells (Fig. 49). The columnar cells may be polarized with their long axes perpendicular to the basement membrane, or they may be stratified, crowded, and disorganized (Fig. 50).

These cells have pink cytoplasm and round to oval nuclei that vary from vesicular to hyperchromatic, with or without nucleoli. In some tumors, goblet cells are found admixed with columnar cells in a ratio similar to that seen in the intestine. In others, the fronds are covered exclusively by columnar or goblet cells. Mitoses may or may not be prominent. The background of papillary tumors is often “dirty,” appearing hemorrhagic, necrotic, and inflammatory (Fig. 49).

Although some papillary tumors are clearly invasive, others remain noninvasive (in situ) over a broad front much like papillary transitional cell carcinoma in situ of the urinary bladder. A few are rather bland cytologically and may resemble a villous adenoma or even normal intestinal mucosa, yet are locally aggressive and destructive.

The colonic type (papillary tubular cylinder cell-II) is composed of well- to moderately differentiated glands and more closely resembles adenocarcinoma of the large intestine than any of the other variants (Fig. 51). At times, cystic (glandular) spaces with intracystic papillary projections are apparent.

The solid variant (papillary tubular cylinder cell-III) is composed of diffuse proliferation of smaller, more cuboidal cells with amphophilic to pink cytoplasm, occasionally with mucin droplets, and round, vesicular nuclei, often with nucleoli. There is little attempt at gland formation (Fig. 52).

The mucinous variant (alveolar goblet cell and signet ring) encompasses three patterns. One is that of small solid clusters of cells, individual glands, signet-ring cells, or short papillary-like fronds, with or without fibrovascular cores, lying in a mucomyxoid matrix. A second pattern is characterized by large, well-formed glands distended with mucus, some of which may rupture and evoke a brisk inflammatory response. The third pattern consists of clusters of

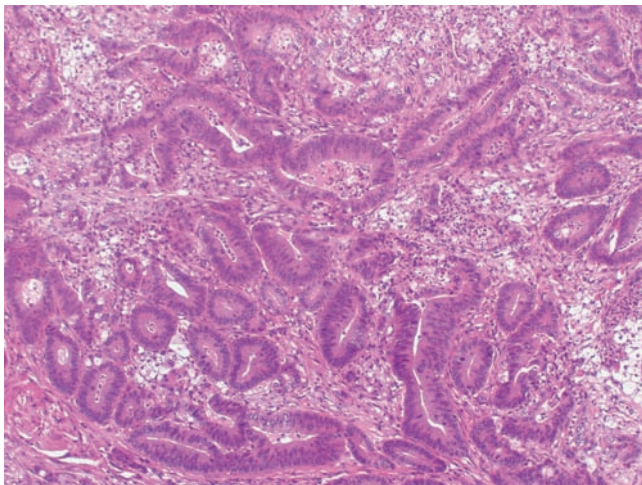


Figure 51 Colonic variant of intestinal-type adenocarcinoma. This type resembles adenocarcinoma of the colon and is composed of well- to moderately differentiated glands (H&E, 100 $\times$).

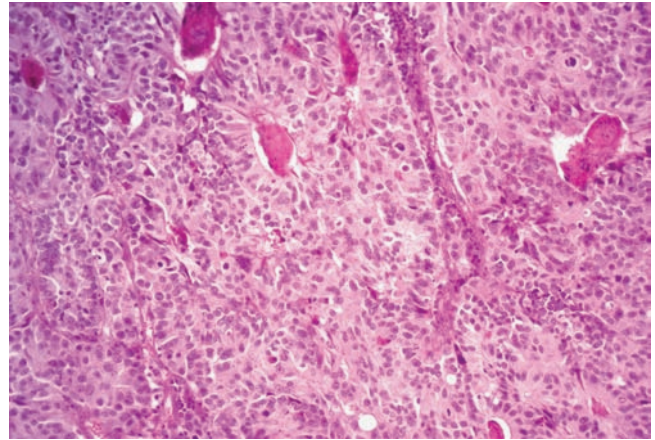


Figure 52 Solid variant of intestinal-type adenocarcinoma. In this type, there is a diffuse proliferation of cells, with only focal gland formation (H&E, 200 $\times$).

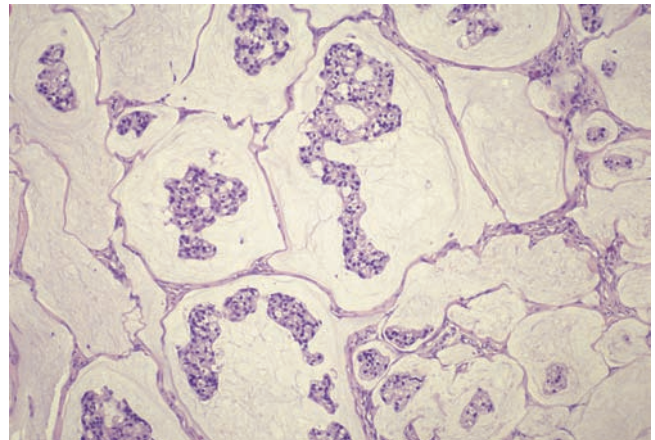


Figure 53 Mucinous variant of intestinal-type adenocarcinoma. Clusters of epithelial cells are lying in a mucinous matrix surrounded by thin fibrous septa (alveolar goblet cell pattern) (H&E, 100 $\times$).

tumors lying in a mucinous matrix surrounded by thin fibrous septa, so-called alveolar-goblet cell variant (Fig. 53).

The mixed pattern (transitional), as the name implies, is composed of two or more of the foregoing growth configurations.

ITACs, regardless of histological type, may contain Paneth and enterochromaffin cells as well as a muscularis mucosa (Fig. 54). The enterochromaffin cells can express a variety of peptides, including gastrin, glucagon, serotonin, cholecystokinin, and *leu-enkephalin* (5,7,25). Although Schmid et al. describe an ITAC that was associated with an elevated

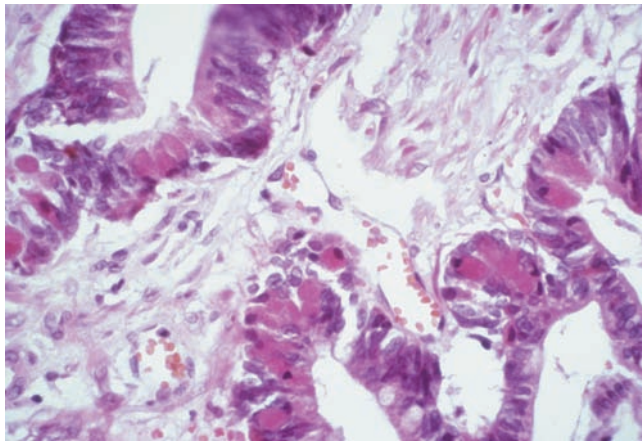


Figure 54 Paneth cells in an intestinal-type adenocarcinoma (H&E, 400 $\times$).

serum level of somatostatin, these tumors virtually never produce a clinically significant endocrine syndrome (5).

Recurrent ITACs may manifest the histological identity of the original tumor, or they may recur or convert into another histological pattern. If they do transform, the transformation is usually from papillary to one of the more aggressive types.

The most common histological types of ITAC seen in woodworkers as well as in sporadic cases are the papillary and colonic variants (11,19).

ITAC, particularly the papillary type, clearly arises from the mucosa of the sinonasal tract (11,40,41). Whether others also arise from the mucosa or from mucoserous glands or their ducts is uncertain. On the basis of the work of Cheng and Leblond and Kirkland, it has been suggested that multidirectional differentiation of a common stem cell could account for the variety of cells (Paneth, endocrine, absorptive, goblet) observed in ITAC (6,42,43). The stem cell, either by direct transformation or by induction of adjacent mesenchyme, might also give rise to the muscularis mucosa noted in a few tumors.

F. Immunohistochemistry

In a collective review of 97 ITACs, we observed that, if performed, 66% were positive for the CK7, 89% for CK20, 89% for CDX2, 96% for synaptophysin, and 53% for chromogranin (44–53). On the basis of these results ITAC in two-thirds of the cases exhibits a characteristic profile of CK7⁺, CK20⁺, CDX2⁺, villin⁺; however, in one-third of cases the profile is CK7⁺, CK20⁺, CDX2⁺, villin⁺.

G. Electron Microscopy

The similarity of ITAC to intestinal tumors extends beyond the light microscopic to the ultrastructural level (5,7). Batsakis et al. have observed glycocaly

bodies in their ultrastructural evaluation of an ITAC of the nasal cavity (7). These structures are thought to be important in identifying tumors of intestinal epithelium or tumors arising from metaplastic intestinal-type epithelium.

H. Molecular-Genetic Data

Despite the similarity of ITAC and adenocarcinoma of the colon at the light microscopic and immuno-histochemical level, there is controversy on whether this relationship extends to the molecular level. Depending on the study, 0% to 29% of ITACs have exhibited K-ras mutations, 0% to 25% H-ras mutations, and 14% to 44% p53 mutations (54–59).

Comparative genomic hybridization (CGH) studies have revealed that ITACs carry a large number of chromosomal gains and losses, including high-level amplifications. The pattern of chromosomal abnormalities in these tumors differs from the pattern in other tumors within the same anatomic area (e.g., squamous cell carcinomas, salivary gland tumors), which may be due to differences in etiology (60).

I. Differential Diagnosis

The differential diagnosis includes a primary non-ITAC, papillary rhinosinusitis, papillary adenocarcinoma of the nasopharynx, and metastatic adenocarcinoma of the gastrointestinal tract.

A primary non-ITAC typically consists of one cell population and, with the possibly exception of a few mucus cells, is devoid of goblet and Paneth cells. It is also positive for CK7 and negative for CK20, CDX2, and villin (Table 27).

Sinusitis, at times, may have a papillary configuration, but in these instances, the papillae are short and blunt and not highly branched as one sees in papillary ITAC. In addition, the background is “clean” in papillary rhinosinusitis, the basement membrane is often thick and hyalinized, the surface cells are ciliated and free of dysplastic changes, and the stroma often has a prominent component of eosinophils.

Features that distinguish papillary ITAC from papillary adenocarcinoma of the nasopharynx are discussed in section XXV of this chapter.

Table 27 Differential Diagnosis of Intestinal and Nonintestinal Adenocarcinoma

Tumor	CK7	CK20	CDX2	Villin	Synaptophysin or chromogranin
Normal mucosa	+	–	–	–	–
ITAC	+/- ^a	+	+	+	+/-
Non-ITAC	+	–	–	–	–
Adenocarcinoma of colon	+/- ^b	+	+	+	–

^aApproximately 66% of ITAC are CK7-positive.

^bApproximately 74% of adenocarcinomas of the rectum are CK7 positive, all other colon adenocarcinomas are usually CK7 negative.

Abbreviation: ITAC, intestinal-type adenocarcinoma.

Metastases to the nasal cavity and paranasal sinuses from a primary adenocarcinoma of the gastrointestinal tract are not common (61,62). In a study of 82 tumors metastatic to the nasal cavity and paranasal sinuses, Bernstein et al. found the most common sites of origin to be the kidney (40 cases), lung (10 cases), breast (8 cases), testis (6 cases), gastrointestinal tract (5 cases; 2 stomach, 2 colon, and 1 rectum), uterus (4 cases), thyroid (3 cases), adrenals (2 cases), cutaneous melanoma (2 cases), and pancreas (2 cases) (61). The maxillary, ethmoid, and frontal sinuses, and the nasal cavity were involved in descending order. In some of these patients, the head and neck metastasis was the initial manifestation of an otherwise clinically occult carcinoma. For this reason, consideration of a gastrointestinal tract adenocarcinoma in all patients with ITACs, especially the colonic variant, would seem prudent, although in the absence of relevant signs and symptoms such studies will generally prove negative.

Immunohistochemistry offers little, if any, help in distinguishing ITAC from a metastatic colorectal adenocarcinoma (see sect. "Immunohistochemistry" above and Table 27). In the past, an immunoprofile of CK7⁺/CK20⁺ was considered characteristic of a colonic adenocarcinoma. More recent studies have shown that the presence or absence of CK7 positivity in colon carcinomas varies according to the level of tumor involvement. Zhang et al. observed in an evaluation of 35 adenocarcinomas of the rectum that 26 (74%) expressed CK7 whereas only 3 of 11 (27%) colon adenocarcinomas proximal to the rectosigmoid colon were positive for CK7 (63).

Since about two-thirds of sinonasal ITACs also express CK7, one cannot rely on this stain entirely to separate ITAC from a metastatic colorectal adenocarcinoma. Immunostains for neuroendocrine markers may offer some possible aid since ITACs tend to contain more endocrine-type cells than colorectal adenocarcinomas and would be expected to stain more extensively (44). When used in tandem, a strongly positive stain for both CK7 and synaptophysin and/or chromogranin would be more supportive of a primary ITAC. Also, if dysplasia or in situ carcinoma is observed in the mucosa adjacent to an ITAC, this would imply that the tumor is primary rather than secondary.

J. Treatment and Prognosis

The clinical course is characterized by repeated local recurrences (53%), with ultimate invasion of the orbit and cranial cavity, but little tendency toward cervical lymph node (mean 8%; range 0–22%) and systemic metastases (mean 13%; range 0–29%) (11). Tumor necrosis with sepsis is often a problem and may be life threatening. In a review of 213 ITACs, Barnes noted that at least 60% of the patients were known to have died of their disease (11). Of those dying, 80% did so within three years of diagnosis. The survival according to histological type is shown in Table 26. Some patients, especially those with papillary ITAC,

may have a slow, "smoldering" disease, only to die of their tumor 10 or more years later.

Treatment consists of surgical excision using a lateral rhinotomy or, at times, even a cranial base approach. The use of radiotherapy is dictated by the extent and resectability of the tumor. An elective neck dissection is not warranted.

Prognosis depends on the histological type, degree of differentiation, stage of the disease, and the adequacy of resection margins. Papillary ITAC, especially grade I or well differentiated, has the best prognosis. It may recur, but it rarely metastasizes. The other types are more virulent, with a greater propensity for dissemination. Over the course of time, a few tumors may change from one histological type into another. This is an ominous finding, signaling a tumor with increased aggressiveness.

Woodworkers seem to have a better prognosis than those individuals with sporadic ITAC. This is probably because the woodworker is under heightened surveillance for this tumor, and in this group, the tumors are more often found in the nasal cavity or ethmoid sinus and, therefore, can be detected earlier by the patient. In contrast, patients with a sporadic tumor are not in early detection programs and have tumors that are relatively more common in the maxillary sinus, which are difficult to detect early.

XXI. NONINTESTINAL-TYPE ADENOCARCINOMA

A. Introduction

Nonintestinal-type adenocarcinomas (Non-ITAC) are uncommon tumors of the nasal cavity and paranasal sinuses that can be divided into low- and high-grade subtypes (1–5). By definition, they do not show histological features of salivary-type neoplasms and do not contain the multiple cell types (absorptive, goblet, endocrine, Paneth) or exhibit the immunoprofile of an ITAC.

Synonyms include low- or high-grade adenocarcinoma, nonenteric adenocarcinoma, seromucinous carcinoma, low-grade papillary adenocarcinoma, terminal tubulus adenocarcinoma, and sinonasal tubulopapillary low-grade adenocarcinoma.

B. Etiology

There are no known environmental or occupational risk factors, although a few cases have occurred in patients with smoking histories.

C. Clinical Features

Low-grade non-ITACs occur over a broad age range (9–89 years, mean about 55–65 years) and exhibit a gender distribution of 1:1 to 1.3:1 in favor of males (1–5). They tend to predilect the nasal cavity and ethmoid sinus and manifest as nasal obstruction and epistaxis. High-grade non-ITACs also occur over a broad age range (15–80 years, mean 59 years) but are

more frequent in males by a ratio of 4 to 5:1 (1). They also tend to be more common in the sinuses rather than in the nasal cavity and are more often associated with pain.

D. Pathology

Non-ITACs usually arise from the mucosa and exhibit a glandular and/or papillary growth (Figs. 55–58). The low-grade variant is composed of small glands, lying back to back, lined by a single layer of epithelial cells. Myoepithelial cells are not seen, mitoses are sparse, and necrosis and perineural invasion are rare to absent. Occasionally, the glands are dilated and/or cystic with intracystic papillary projections. The

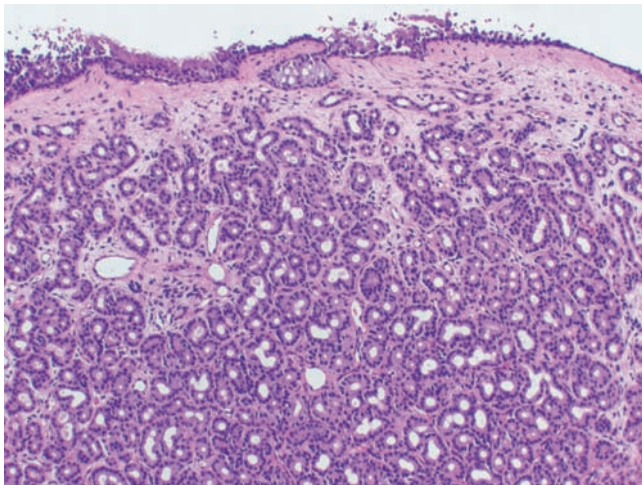


Figure 55 Nonintestinal-type adenocarcinoma, low grade, composed of well-differentiated glands lying back to back (H&E, 40 $\times$).

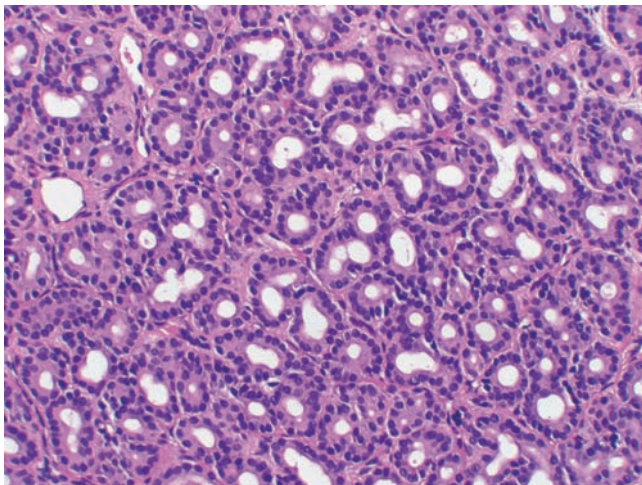


Figure 56 Higher magnification of the tumor shown in Fig. 55. The glands are lined by a single layer of epithelial cells. Myoepithelial cells are absent (H&E, 400 $\times$).

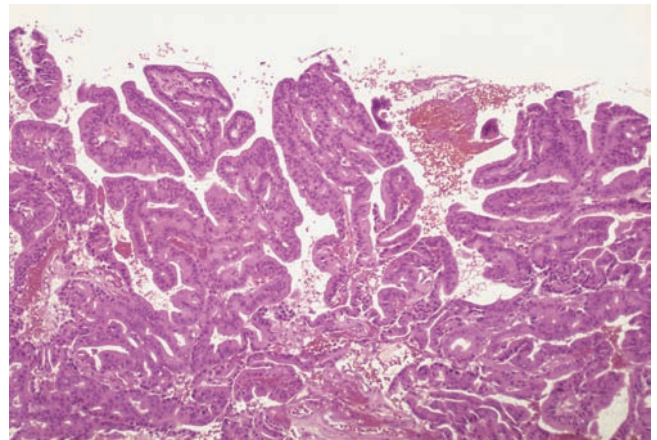


Figure 57 Nonintestinal-type adenocarcinoma, low grade, with a papillary pattern (H&E, 100 $\times$).

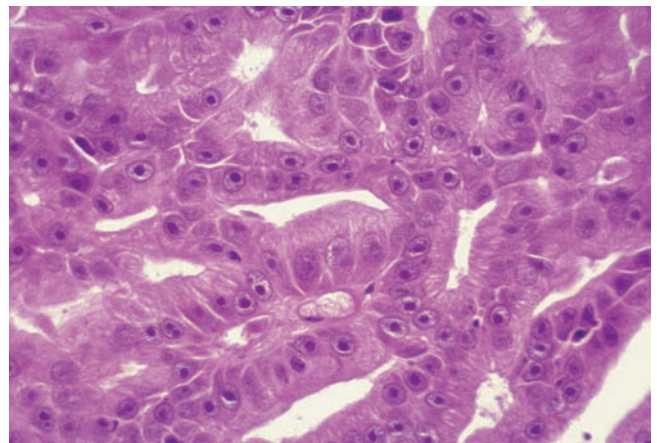


Figure 58 Higher magnification of the tumor shown in Fig. 57. The tumor is composed of one cell type as opposed to several different cells that may be seen in some intestinal-type adenocarcinomas. In this instance, the cells have pink cytoplasm and large vesicular nuclei with prominent nucleoli. Mitoses are sparse (H&E, 400 $\times$).

surface of the tumor may be either sessile or papillary (Figs. 55 and 57). Not infrequently, a tumor will show focal areas suggestive of an acinic cell carcinoma or exhibit oncocytoid changes. A few tumors may contain small intracytoplasmic mucin vacuoles.

High-grade tumors, in turn, are more pleomorphic and exhibit increased mitoses, necrosis, and perineural invasion. They are also less glandular or papillary and often grow in a solid or sheet-like pattern.

E. Immunohistochemistry

Non-ITACs are positive for CK7 and negative for CK20, CDX2, and villin (3,5,6). Although some tumors

stain for S-100 protein, they are otherwise negative for myoepithelial and neuroendocrine markers (3).

F. Differential Diagnosis

The differential diagnosis includes ITAC, inverted Schneiderian papilloma or OSP, and a salivary-type adenoma.

Non-ITAC has a characteristic immunoprofile of CK7⁺, CK20⁻, CDX2⁻, villin⁻ which contrasts with the CK7^{+/+}, CK20⁺, CDX2⁺, villin⁺ profile of ITAC (Table 27). ITAC is also occasionally positive for neuroendocrine markers, while the non-ITAC is negative.

The inverted Schneiderian papilloma is composed of squamous and/or respiratory epithelium, which is not seen in non-ITAC. The OSP is uniformly composed of oncocyctic epithelium, with prominent intraepithelial mucin-filled cysts and microabscesses (Figs. 36 and 37). While oncocyctic cells may be seen in non-ITAC, intraepithelial cysts and microabscesses are not. Salivary-type adenomas contain myoepithelial cells, which are not observed in non-ITACs.

G. Treatment and Prognosis

Low-grade non-ITAC can usually be managed by surgery alone, either through an endoscope or a medial maxillectomy, whereas high-grade tumors often require both surgery and radiation.

Low-grade non-ITACs are characterized by 20% to 30% incidence of local recurrences (usually within 2–4 years of therapy) and rare to absent cervical lymph node and distant metastases (1–5). Death from disease is rare (1). High-grade tumors, on the other hand, are aggressive, with a 30% incidence of distant metastases and a 20% three-year survival (1).

XXII. SALIVARY-TYPE NEOPLASMS

A. Introduction

Mucoserous glands are present throughout the sino-nasal tract and are particularly abundant in the nasal cavity along the lateral wall, including the turbinates, and to a lesser extent on the nasal septum (1). They are, however, relatively uncommon in the sinuses.

Salivary-type neoplasms may arise not only from these glands but also the surface mucosa (2). Despite the abundance of glands, tumors derived from them, with the exception of adenoid cystic carcinoma, are scarce, and risk factors are largely unknown.

A brief summary of some of these neoplasms follows. A more detailed account of their clinicopathological features can be found in the chapter “Diseases of the Salivary Glands.”

B. Pleomorphic Adenoma

Pleomorphic adenoma of the sinonasal tract occurs primarily in the nasal cavity and only rarely in the sinuses (3–5). In a review of 40 cases, the largest series

to date, Compagno and Wong noted that 25 originated from the bony or cartilaginous nasal septum, with most having a broad base rather than a pedicle attachment. Eight arose from the lateral wall, usually involving a turbinate, and in seven the exact site of origin within the nasal cavity could not be determined (3). The sinuses were not involved in any case, either primarily or secondarily.

Intranasal pleomorphic adenomas occur over a broad age range (3–82 years, mean 42 years) and involve both genders about equally (3,4). Unilateral nasal obstruction and episodic epistaxis are the usual symptoms. On imaging, one sees an expanding, heterogeneous mass that fills the cavity and may even erode or destroy bone (3,6).

Grossly, the tumors appear exophytic, polypoid, or dome shaped and have ranged from 0.5 to 7.0 cm in greatest dimension. Microscopically, they are more cellular than the “usual” pleomorphic adenoma. Rare examples, which have ossified or even exhibited focal skeletal muscle differentiation have been described (5,7).

In the series of Compagno and Wong, 31 of 34 patients (90%) available for follow-up (mean 7.4 years) showed no evidence of local recurrence, regardless of excisional procedure used (intranasal vs. wide excision) (3).

A few examples of carcinoma expleomorphic adenoma of the nasal cavity have been documented (8).

C. Oncocyctic Tumors

Oncocyctic tumors of the nasal cavity and paranasal sinuses, comparable to those seen in the major salivary glands, are rare. They are more common in the nasal cavity than the sinuses and frequently predilect the nasal septum.

In our review of 15 cases, nine occurred in males and five in females. The gender of one case was not indicated (9–13). The ages ranged from 23 to 86 years (mean 58 years). All presented with nasal stuffiness/obstruction, rhinorrhea, and/or epistaxis.

Some of the tumors have been as small as 5 mm (9), and most on microscopic examination are of the solid type of oncocytoma. There are some who state that all oncocyctic lesions in this location should be considered as low-grade carcinomas, despite their histological appearance. We wish to point out that any benign tumor in this relatively closed environment may erode bone and exhibit necrosis, e.g., IP, angiofibroma, and are not absolute signs of malignancy. In our opinion, an oncocyctic lesion should only be considered as malignant if it shows unequivocal invasion (not erosion of bone), increased mitotic activity (especially atypical mitoses), pleomorphism, perineural invasion, and/or metastasis.

The differential diagnosis includes an oncocytoid/oncocyctic carcinoid tumor, a metastatic renal cell carcinoma, and a metastatic oncocyctic (Hürthle cell) carcinoma of thyroid. A carcinoid tumor, in contrast to an oncocytoma, is positive for synaptophysin and/or

chromogranin. Vimentin, CD10, and renal cell carcinoma antigen are useful immunohistochemical markers that aid in separating metastatic renal cell carcinoma from an oncocytoma. Renal cell carcinoma is positive for these stains while the oncocytoma is negative (14). Oncocytic thyroid carcinoma is usually positive for thyroglobulin and thyroid transcription factor, while oncocytoma is negative for these markers.

D. Acinic Cell Carcinoma

Acinic cell carcinomas occur primarily in the parotid gland and only exceptionally in the sinonasal tract. In a review of 14 cases, Neto et al. noted that the nasal cavity was more often involved than the sinus and that seven (50%) arose from either the inferior or middle turbinate (15). The patients, eight females and six males, ranged in age from 42 to 76 years (median 59 years). Nasal obstruction was by far the most frequent complaint.

The tumors ranged in size from 1 to 6 cm and were most often treated by surgery alone. Three patients also received postoperative radiation. None underwent a neck dissection. At least one patient developed local recurrence but was stated to be disease free 12 years later after additional therapy.

The differential diagnosis might include a non-ITAC (seromucinous), which infrequently shows a focal (rather than diffuse) acinic cell pattern. Acinic cell carcinoma, however, contains periodic acid-Schiff, diastase-resistant granules that are not typically seen in the non-ITAC.

E. Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is the most frequent salivary-type neoplasm of the sinonasal tract. Although slowly growing, it is locally aggressive and relentless in its progression with death from disease often exceeding 10 years or more (16–19).

ACC of the sinonasal tract occurs over a broad age range (18–82 years, mean about 45–55 years) and exhibits a gender distribution of 1:1 to 2.5:1 in favor of males (17,19). In one series of 35 cases, 19 tumors arose in the maxillary sinus, 10 in the nasal cavity, and 6 in the ethmoid sinus (19). Symptoms include nasal obstruction, epistaxis, toothache, swelling and pain of the premaxilla and palate, paresthesias, proptosis, visual disturbances, trismus, and/or headache. Tumors, especially those of the maxillary sinus, are often advanced at the time of diagnosis and staged as T3 or T4 (Figs. 59–61).

Surgery with adjuvant radiation is the usual treatment. Following therapy, approximately 50% to 75% of patients will experience local recurrence usually within five years, and 3% to 5% will experience cervical lymph node metastasis, and 30% to 35% will have distant dissemination of tumors to the lungs and bones. The overall 10-year survival is about 40% to 55% at best (17,19).

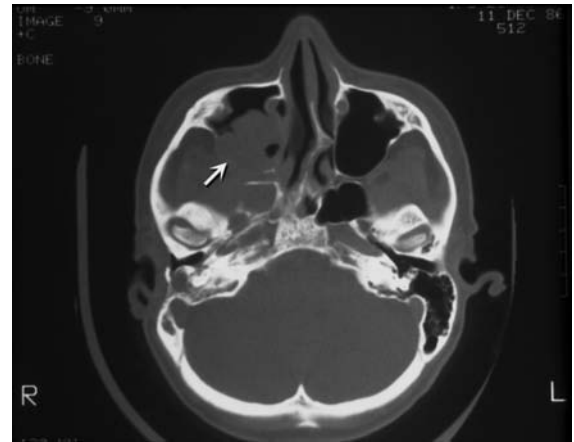


Figure 59 Image of an adenoid cystic carcinoma of the right maxillary sinus (*arrow*). The tumor occupies most of the sinus and involves the medial and posterior walls.

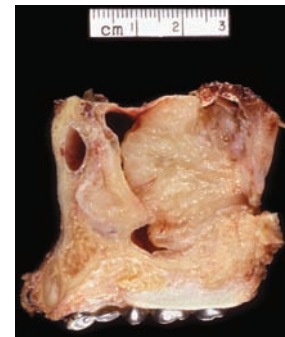


Figure 60 Gross picture of the resected adenoid cystic carcinoma shown in Fig. 59. The tumor is solid and deceptively well circumscribed.

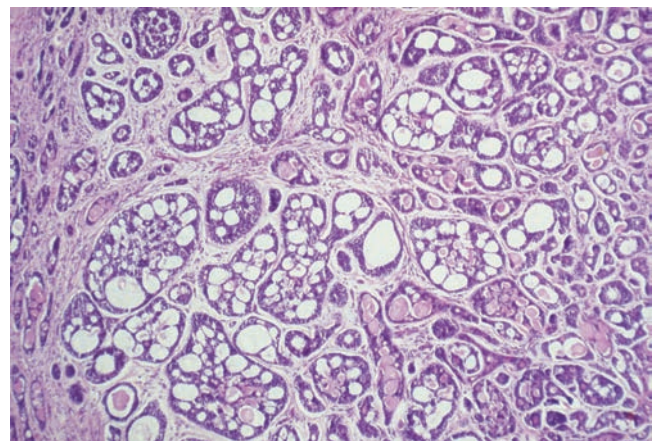


Figure 61 Microscopic view of the adenoid cystic carcinoma in Figs. 59 and 60 showing the classic cribriform pattern of tumor cells (H&E, 100 $\times$).

F. Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is an uncommon tumor in the sinonasal tract. In one review of 220 carcinomas of the nasal cavity and paranasal sinuses, only four (1.8%) were classified as MECs (20). The largest single series to date consists of 19 cases (21). These occurred in 10 females and 9 males aged 15 to 75 years (mean 53 years). Ten cases arose in the nasal cavity, six in the maxillary sinus, and in the remaining three, both nasal cavity and sinus were involved. The tumors had a mean size of 2.4 cm and manifested clinically as a “mass,” nasal obstruction, or epistaxis. Most of the tumors were low grade ($N = 10$), with intermediate ($N = 6$) and high grade ($N = 3$) comprising the remainder.

Surgery, at times supplemented with radiation, was the usual treatment. Of the 19 patients, six developed a recurrence and five died of disease (mean 2.4 years). The remaining 14 patients were either alive ($N = 9$) or had died ($N = 5$) of unrelated causes (21).

The differential diagnosis includes necrotizing sialometaplasia and adenosquamous carcinoma (ASC). In necrotizing sialometaplasia, in contrast to MEC, the lobular architecture of the mucoserous glands is maintained, and there is no perineural invasion. The distinction between MEC and ASC in the sinonasal tract is more problematic. In sites outside the sinonasal tract, the presence of an in situ surface (mucosal) component generally indicates an ASC. In the sinonasal tract, MEC can arise from and/or involve the surface (mucosa) (2,21), and as a consequence, this discriminating feature is lost. MEC, as opposed to ASC, contains multiple cell-types—epidermoid, mucous, intermediate, and clear—and shows little evidence of keratinization or keratin pearls.

G. Other Tumors

Additional salivary-type neoplasms have also been described in the nasal cavity and paranasal sinuses, though rarely. Among these are included myoepitheliomas, epithelial-myoepithelial carcinoma, polymorphous low-grade adenocarcinoma, and basal cell adenocarcinoma (22–25).

H. Nasopharynx

Salivary-type neoplasms of the nasopharynx are rare and not well documented. Kuo and Tsang have described 15 cases. These included eight MECs, two adenoid cystic carcinomas, four nonspecific adenocarcinomas, and one composite adenocarcinoma—undifferentiated carcinoma (26).

XXIII. MALIGNANT MELANOMA

A. Introduction

Fifteen to 25% of all MMs occur in the head and neck and, of these, 6% to 8% involve the mucus membranes of the upper aerodigestive tract (1–7). Malignant melanomas of the mucus membranes of the nasal cavity

and paranasal sinuses are uncommon. They account for less than 1% of all MMs and 2% to 8% of all malignant neoplasms of the sinonasal tract (7–14).

The incidence of cutaneous MMs is rising faster than any other cancer and, as such, has become an important public health issue. Between 1950 and 2000, the incidence rose an astonishing 697%! (15,16). According to Rigel, the lifetime risk of an individual in the United States to develop MM was 1:1500 in 1935 (17). By 1980, the risk had increased to 1:250 and by 2000, it was 1:75. In contrast, the incidence of mucosal MMs has remained remarkably stable over the last several decades (6,18).

B. Etiology

Mucosal MMs of the sinonasal tract arise from melanocytic precursors that originate in the neural crest. During migration these cells normally populate the mucus membranes but may also remain confined to the stroma (lamina propria). Accordingly, some primary mucosal MMs may arise from these stromal precursors and not exhibit any junctional or in situ changes of the mucosa (19,20).

Although excessive exposure to sunlight and genetic factors (dysplastic nevus syndrome) are important in the etiology of cutaneous MM, there are no known risk factors for mucosal MM (21,22). There are, however, sporadic reports of mucosal MMs associated with preexisting “melanosis” or occurring somewhat more frequently in certain ethnic groups (Ugandan Africans), suggesting the possibility that ectopic melanin production and race may be potential factors (23,25). Whether melanosis in some instances represents a true focal increase in melanin production or an unrecognized radial growth phase of a preexistent melanoma is not always clear.

There is also a recent report raising the possibility of whether sinonasal MMs may be related to formaldehyde exposure (20).

C. Clinical Features

MMs occur more often in the nasal cavity than in the sinuses. In a collective review of 604 cases in which the site of origin was indicated, 71% arose in the nasal cavity, 16% in the sinuses, and 13% involved both areas (Table 28) (7,9,24,26–48). In the nose, the most common sites of origin are the anterior septum and inferior and middle turbinates (Fig. 62). When confined to the sinuses, the maxillary is most often involved, followed by the ethmoid. The frontal and sphenoid sinuses are rarely affected.

The vast majority of patients at the time of diagnosis are older than 50 years (mean 60–70 years) (19,26,27,32–39,43,46). Only 10% to 20% occur in individuals younger than 50 years. Although some studies have shown either a male or female predominance, a collective review of 268 cases reveals only a slight male predominance (54%; M/F = 1.2:1) (9,26,27, 32–39,43,46). Most patients are white, but 5% to 16% are black (20,26,35). Nasal obstruction and epistaxis,

occasionally accompanied by swelling of the nose or cheek, are the usual presenting complaints. Pain, however, is uncommon.

On physical examination, the tumors are sessile or polypoid, pink, white, brown, or black and average 1 to 4 cm (Fig. 62). In some instances, they are

Table 28 Distribution of 604 Malignant Melanomas of the Nasal Cavity and Paranasal Sinuses

References	Total no. of cases	Nose	Sinus	Sinonasal
Moore (7)	10	9	1	0
Holdcraft (26)	39	21	7	11
Freedman (27)	47	29	18	0
Conley (28)	18	12	6	0
Eneroth (29)	24	16	0	8
Shah (30)	45	39	6	0
Snow (31)	11	11	0	0
Cove (24)	1	0	0	1
Lund (9)	36	33	3	0
Bethelsen (32)	20	20	0	0
Blatchford (33)	6	6	0	0
Panje (34)	10	9	1	0
Trapp (35)	15	11	4	0
Suen (36)	1	1	0	0
Huntrakoon (44)	2	0	1	1
Going (37)	1	0	1	0
Gilligan (38)	28	16	4	8
Franquemont (39)	14	4	7	3
Stern (40)	20	12	8	0
Guzzo (41)	26	26	0	0
Thompson (42)	16	13	3	0
Kingdom (43)	17	10	7	0
Loree (45)	18	14	4	0
Brandwein (46)	21	12	5	4
Thompson (20)	106	64	3	39
Prasad (47)	39	29	4	6
Manolidis (48)	13	10	3	0
Total	604	427	96	81
	(100%)	(71%)	(16%)	(13%)



Figure 62 Deeply pigmented malignant melanoma involving the inferior nasal turbinate. The thick arrow shows small, multifocal areas of additional melanoma. The thin arrow depicts an area of melanosis.

diffusely hemorrhagic and fill the entire nasal cavity. Bone destruction may or may not be apparent on radiological studies.

At the time of diagnosis, 0% to 20% of patients will have positive cervical lymph nodes, especially around the submandibular gland (9,27,28,30,32,34,35,38,40,42,43). Only 6%, however, will have distant metastases (9,42).

D. Pathology

MMs of the sinonasal tract, histologically, resemble their cutaneous counterparts and, as such, are composed of epithelioid or spindle cells arranged in small clusters (thèques) or sheets (Figs. 63 and 64). Mitoses,

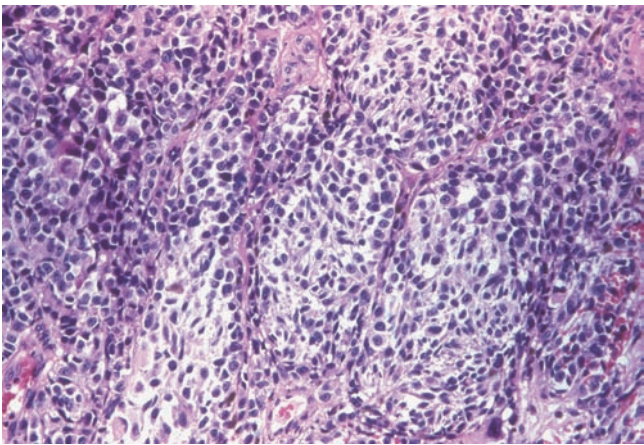


Figure 63 Amelanotic malignant melanoma of the nasal cavity composed of epithelioid cells arranged in an alveolar pattern (H&E, 200×).

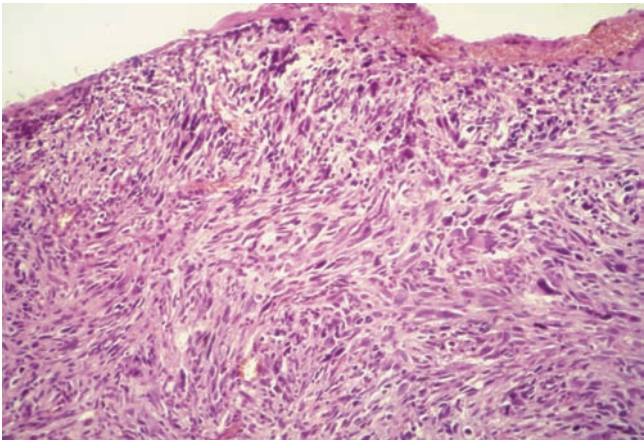


Figure 64 Amelanotic malignant melanoma of the nasal cavity composed of spindle cells. Note the vague storiform pattern. Such tumors may be confused with a malignant fibrous histiocytoma or other soft-tissue sarcomas (H&E, 100×).

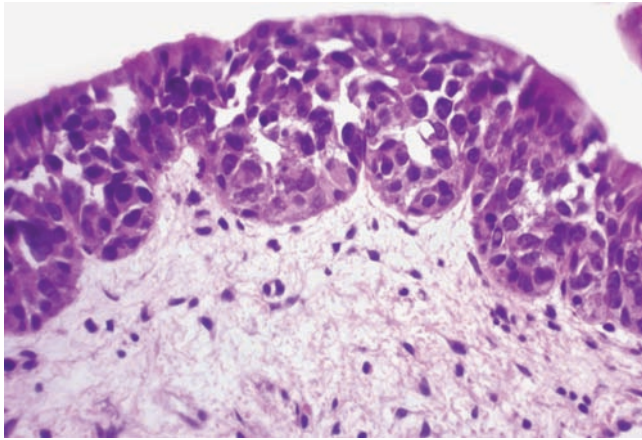


Figure 65 In situ malignant melanoma of the nasal cavity (H&E, 400 $\times$).

pleomorphism, intranuclear inclusions of cytoplasm, necrosis, and lymphatic, vascular, and perineural invasion are additional, although inconsistent, features.

Because of extensive ulceration, junctional or pagetoid invasion of the overlying mucosa is seen in only 9% to 44% of cases (20,26,39,49) (Fig. 65). Ten to 30% of tumors are also amelanotic, requiring special tissue stains [S-100 protein, HMB-45 etc.] and a high index of suspicion for diagnosis (26,27).

Desmoplastic mucosal MMs, though rare, have also been described, primarily in the oral cavity but also in the sinonasal tract (50).

E. Immunohistochemistry

Immunohistochemical evaluation of sinonasal MMs using the standard melanoma markers have shown that 91% to 95% are positive for S-100 protein, 76% to 98% for HMB-45, 78% to 100% for tyrosinase, 65% to 100% for melan-A, and 57% to 91% for microphthalmic transcription factor (20,51). S-100 protein and tyrosinase are the best stains to identify desmoplastic mucosal MMs, while HMB-45 is negative in most desmoplastic and many spindle cell MMs (51).

F. Molecular-Genetic Data

Van Dijk et al. examined 14 sinonasal MMs by comparative genomic hybridization (CGH) and observed two remarkably consistent alterations (52). First, chromosome arm 1q was gained in all tumors, and all tumors harbored a gain of 6p, a loss of 6q, or both. Second, gains of 1q, 6p, and 8q occurred frequently in combination with a loss of copy number or a normal copy number of the opposite chromosome arm, suggesting isochromosome formation. Comparing these CGH results, the authors concluded that sinonasal melanomas harbor a more consistent CGH pattern than other melanoma types and subtypes. This as well as other studies suggest that there may be several

distinct genetic-molecular pathways that lead to different types of MMs (52,53).

G. Differential Diagnosis

MM is one of the great mimickers in pathology. Under appropriate conditions, it can be mistaken for a variety of tumors, including carcinomas, sarcomas, and lymphomas (54,55). This is especially true in the sinonasal tract where the tumor is rare, often fails to show junctional activity, frequently is amelanotic, and occasionally grows in a spindle pattern.

The biggest problem in differential diagnosis rests, therefore, in simply failing to consider MM as a possibility. Once considered, the diagnosis can easily be established by appropriate immunohistochemical stains or ultrastructural evaluation.

Amelanotic spindle cell melanomas of the sinonasal tract often grow in large fascicles and are frequently mistaken for a fibrosarcoma or malignant schwannoma. They may also exhibit a storiform pattern and be confused with a malignant fibrous histiocytoma (Fig. 64). As a general rule, one should never make a diagnosis of a soft-tissue sarcoma adjacent to a mucous membrane in the head and neck without first excluding a spindle cell carcinoma, an amelanotic MM, and a myoepithelial neoplasm.

A metastasis from a cutaneous MM to the sinonasal tract must also be considered in the differential diagnosis (56–60). The incidence of cutaneous MM metastasizing to the mucosal surfaces of the head and neck is 0.2% to 0.7% if clinical data are used and 2% to 8% if autopsy studies are included (56,58,60–62). When cutaneous MMs disseminate to the mucous membranes of the head and neck, the primary is most often located on the trunk (55–62% of cases), followed by extremities (24–27%), and head and neck (18–24%) (58,60). More than 60% of the mucosal metastases will appear within two years of diagnosis of the cutaneous lesion and about 60% to 65% of the patients will also have evidence of disseminated disease at the time of diagnosis of the mucosal lesion. Junctional activity in the overlying or adjacent mucosa, if present, in conjunction with the clinical history, distinguishes primary mucosal MM from metastatic disease (60). However, as previously mentioned under “Etiology,” some primary sinonasal MMs may also arise from stromal melanocytic precursors and, accordingly, will not show junctional or in situ mucosal changes.

H. Treatment and Prognosis

The treatment of choice for sinonasal MM is surgery. Once considered radioresistant, radiation is now considered by some and denied by others to be an important adjuvant in achieving local control and may even have merit as a prime modality in selected patients (20,63–66). An elective neck dissection for sinonasal MM is usually not warranted (40). Chemotherapy is, at present, employed principally in the treatment of disseminated disease and for palliation.

Local recurrence (40–85%) and distant metastasis (30–70%), rather than regional lymph node metastasis (10–30%), are responsible for most treatment failures and deaths (9,27,28,30,32,34,35,38,40,42,43,67). The five-year survival rate is about 20% to 30% (range 6–48%) (9,26,28,30,32,34–36,40,41,67). The average interval from initial treatment to local recurrence in three reported series has ranged from 9 to 13 months (34,40,43). Local recurrence following seemingly adequate excision is ascribed to the presence of intralesional lymphatic and blood vessel invasion seen in many tumors.

Local recurrence and distant metastasis are ominous signs. Most patients who fail locally eventually die of their disease, and of those who develop systemic disease, the average survival after metastasis is only six months (30,34,40). The lungs, liver, brain, bones, and spinal cord are the most frequent sites of dissemination, but occasionally unusual areas, such as the small intestine and heart, may also be involved (62,68,69).

Clark staging of mucosal MMs is not possible because of the absence of comparable landmarks within the mucosa and lamina propria of the upper respiratory tract that are present in the dermis. The Breslow thickness, the single most important histological prognostic factor in cutaneous MM, has not been found to be useful in mucosal MMs of the head and neck (20,47). In lieu of these two parameters, Prasad et al. have proposed a three-level microstaging system that seems to correlate with prognosis (Table 29) (47). In a review of 61 mucosal MMs (39 sinonasal, 20 oral, 1 pharyngeal, and 1 laryngeal), they observed the median survival to be 138 months for Level I, 69 months for Level II, and 17 months for Level III (47).

The tumor-node-metastasis (TNM) classifications for nasal cavity, paranasal sinuses, and skin are not readily applicable for mucosal MMs. As a result, Thompson et al. have proposed a modification shown in Table 30 (20). Another more simplified clinical staging system uses three stages—stage I (localized disease), stage II (locoregional disease), and stage III (distant disease at presentation) (70).

Local recurrence, and tumors composed of undifferentiated cells with a sarcomatoid and pseudopapillary architecture, and more than 10 mitoses per 10 HPFs are indicators of a poor prognosis (20,47).

Table 29 Prasad's Microstaging of Mucosal Malignant Melanomas of the Head and Neck

Level	Definition
I	Melanoma in situ without evidence of invasion or with only microinvasion (defined as invasive individual or clusters of <10 atypical melanocytes near the epithelial junction)
II	Invasion limited to the lamina propria
III	Deep tissue invasion into skeletal muscle, bone, or cartilage

Source: From Ref. 47.

Table 30 Proposed TNM staging of Sinonasal and Nasopharyngeal Mucosal Malignant Melanomas

Stage	Definition
Primary tumor	
T1	Single anatomic site
T2	Two or more anatomic sites
Regional lymph node	
N1	Any lymph node metastasis
Distant metastasis	
M1	Distant metastasis
Stage grouping	
Stage I	T1, N0 M0
Stage II	T2, N0 M0
Stage III	Any T, any N, M1
Stage IV	Any T, any N, M1
T, primary tumor.	
TX, primary tumor cannot be assessed.	
T0, no evidence of primary tumor	
T1, tumor limited to a single anatomic site. A single anatomic site is defined as one of the following: nasal cavity, maxillary sinus, frontal sinus, ethmoid sinus, sphenoid sinus, nasopharynx. Subsites, such as septum, lateral wall, turbinate, nasal floor, or nasal vestibule are not separately considered.	
T2, tumor involving more than one anatomic site. More than one anatomic site is defined by tumor involvement of more than one anatomic site (although not subsite) as cited above, including any extension into subcutaneous tissues, skin, palate, pterygoid plate, floor, wall, or apex of the orbit, cribriform plate, infratemporal fossa, dura, brain, middle cranial fossa, cranial nerves, clivus.	

Data derived from Ref. 20.

Abbreviation: TNM, tumor-node-metastasis.

XXIV. NASOPHARYNGEAL CARCINOMA

A. Introduction

NPC is defined by the WHO as “a cancer arising in the nasopharyngeal mucosa that shows light or ultrastructural evidence of squamous differentiation. It encompasses squamous cell carcinoma, nonkeratinizing carcinoma (differentiated or undifferentiated) and basaloid squamous carcinoma. Adenocarcinoma and salivary gland carcinoma are excluded” (1).

It has a very distinctive geographic and ethnic distribution (see “Etiology” below). On a worldwide basis, it is a relatively rare tumor, with an estimated 65,000 new cases per year, or 0.6% of all cancers (1).

B. Anatomy

Anatomically, the nasopharynx is a small, relatively inaccessible space that represents the cranialmost

portion of the pharynx. It averages 2 to 3 cm anteroposteriorly and 3 to 4 cm vertically and transversally, with considerable individual variation (2).

Anteriorly, it communicates with the nasal cavity through the posterior choanae. Superiorly, the roof is formed by the base of the skull and the undersurface of the sphenoid sinus. Posteriorly, the wall is composed of the ventral surfaces of the first and second cervical vertebrae. Inferiorly, it communicates with the oropharynx, or if the soft palate is closed, the superior surface of the soft palate forms the floor. Laterally, the orifices of the eustachian tubes are found, each partially surrounded by a cartilaginous elevation referred to as the torus tubarius. Medial to this elevation is the pharyngeal recess or fossa of Rosenmüller, which is a slit-like space of variable size and depth.

Histologically, the nasopharynx is lined by both ciliated respiratory and stratified squamous epithelium, with respiratory epithelium predominating near the posterior choanae and squamous epithelium on the posterior and lateral walls, with areas of epithelial transition. The nasopharynx is part of Waldeyer's ring and, accordingly, contains abundant lymphoid tissue, with occasional germinal centers and crypts. Mucoserous glands are seen but are not prominent.

C. Etiology

The etiology of NPC is multifactorial and relates to the interaction of race, genetics, environment and the EBV. Although the incidence is declining, it is still one of the most frequent cancers in Chinese, especially among those who reside in southern China in the province of Kwantung and in Hong Kong (20–30 cases per 100,000 population per year), and also occurs with increased frequency in North Africa and among Alaskan Eskimos, Indians, and Aleuts (3,4). In most other countries, it is an uncommon tumor (less than one case per 100,000 population per year) (5). As the Chinese immigrate to other low-frequency countries, the incidence of NPC diminishes with successive generations, but even then, the risk of NPC remains greater than that of the new host population (6,7).

Human leukocyte antigens (HLA) may also be important etiological or prognostic indicators in NPC. The association, however, is sometimes confusing and contradictory and may vary with ethnic group and country. In a meta-analysis of southern Chinese, Goldsmith et al. observed a positive association for NPC risk and HLA-A2, HLA-B14, and HLA-B46 and a negative association for HLA-A11, HLA-B13, and HLA-B22 (8). A genetic predisposition is also supported by the observation that individuals who have a first-degree relative with NPC are also at risk for developing tumor (9).

Dietary factors, especially preserved foods that contain a high content of nitrosamines such as Cantonese salted fish, are also implicated and especially if the individual consumes such food on a regular basis during the first decade of life (10–12).

The EBV has been incriminated in the etiology of NPC (especially the nonkeratinizing tumors, WHO II

and III) by the fact that high antibody titers to the virus are found in most patients regardless of geographic location. The association was strengthened when EBV DNA and EBV-associated nuclear antigens were found in the epithelial cells of NPC and not in the lymphoid component of the tumor (13,14). As the tumor burden increases so does the antibody titer.

It has been suggested that the HPV, as well as cigarette smoking, alcohol, and formaldehyde exposure, may play a role in the etiology of the keratinizing type of NPC (WHO I) (15–18). Other factors that may impact on the risk of NPC include an occupational exposure to wood dust and a history of chronic nose and throat problems (rhinosinuitis) (1,19–21).

D. Clinical Features

NPC occurs in all age groups with a peak incidence between 30 and 50 years of age. Some regions have observed a bimodal distribution, with one peak between 10 to 20 years of age and another at 40 to 60 years (22–33). The ratio of males to females is rather consistent, regardless of geographic location, and is about 2 to 3:1.

Patients typically present with nasal obstruction, epistaxis, serous otitis media, or an asymptomatic neck mass (usually in the apex of the posterior cervical triangle or superior jugular area). At the time of diagnosis, 10% to 20% will also have a cranial nerve dysfunction (especially III, IV, V, and VI) and 60% to 85% will have positive cervical lymph nodes, of which 35% to 45% will be bilateral (2,34–36). Less than 5%, however, will have distant metastasis. In rare instances, NPC may present with dermatomyositis or manifest with inappropriate secretion of antidiuretic hormone or Cushing's syndrome secondary to ectopic adrenocorticotrophic hormone production (37–39).

The most common site of origin in the nasopharynx is the lateral wall in the region of the fossa of Rosenmüller, adjacent to the opening of the eustachian tube followed by the posterior-superior wall. In a review of 437 patients, Skinner et al. observed that 78% of the tumors were lateral in origin and equally distributed between the right and left sides of the nasopharynx, 12% were central in origin, 5% were occult with a normal-appearing nasopharynx, and 5% were too large to determine their origin (34).

The clinical appearance of the tumor, as viewed through an endoscope, is highly variable. In a retrospective review of 209 patients, Dickson noted that 74% of the carcinomas were exophytic, 14.4% infiltrative, and 6.7% ulcerative; in the remaining 4.8%, the tumor was not described (7).

In countries where the incidence of NPC is low, the diagnosis is often not considered. The symptoms are regarded as trivial and largely ignored, which accounts for the advanced stage when first recognized. Once the diagnosis is entertained, the patient should have a thorough examination, including nasopharyngoscopy (40). Imaging studies are crucial for proper staging, planning of treatment, and selecting the most appropriate site of biopsy. Plain radiography, however,

lacks sensitivity and specificity. Computed tomography and magnetic resonance imaging are much preferred and very helpful in defining the extent of skull base invasion, present in about 25% to 30% of cases (41).

Cytology, both exfoliative and fine needle aspiration, may also have a role in the diagnosis of NPC. The value of exfoliative cytology is, however, controversial, with overall diagnostic accuracy rates ranging anywhere from 26% to 89% (42). Fine needle aspiration of enlarged cervical lymph nodes has, on the other hand, opened a new vista in diagnosis. It not only provides material that may be diagnostic but also provides cells or tissue fragments that can be analyzed by in situ hybridization and/or the polymerase chain reaction for the presence of the EBV (43–46).

Patients with NPC frequently develop antibodies to a variety of EBV antigens, particularly immunoglobulin A (IgA) antibodies, to the viral capsid antigen and early antigen. As the tumor burden increases, so does the antibody titer. Consequently, the viral titer can be used not only as a diagnostic tool to screen populations at risk but also to monitor therapy (47–51).

More recently, it has been shown that the detection of EBV genomic LMP-1 by nasopharyngeal cotton swab and polymerase chain reaction amplification is a valuable tool for screening and early detection of NPC. Hao et al. indicate that the procedure has a 92% positive predictive value and a 97% negative predictive value (52).

Once the diagnosis is established, it then becomes necessary to determine the extent or stage of the tumor. In the past, there were two competing staging systems—the AJCC and the Ho. Each had its own advantages and disadvantages (53–56). The new sixth edition (2002) of the *AJCC Cancer Staging Manual* has incorporated the best features of both and is now emerging as the most preferred (Table 31) (57).

E. Pathological Features

To standardize the confusing histological terminology of NPC, the WHO in 1978 proposed that these tumors be divided into three categories: squamous cell carcinoma, nonkeratinizing carcinoma (NKC), and undifferentiated carcinoma (58). In 1991, the WHO slightly modified this classification and once again in 2005 (Table 32) (1,59).

The term “squamous cell carcinoma,” also sometimes referred to as WHO I, is used for those tumors that show definite evidence of squamous differentiation (intercellular bridges, keratinization) over most of its extent and is associated with a desmoplastic reaction (Fig. 66). It can be graded as well, moderately, or poorly differentiated, has a weak relationship to EBV, tends to remain localized, and has a variable response to irradiation (60). It rarely occurs in individuals younger than 40 years.

The differentiated NKC (WHO II), as the name implies, shows no evidence of keratinization. The cells are stratified and have an appearance similar to that of transitional cell carcinoma of the urinary bladder

Table 31 AJCC Staging of Nasopharyngeal Carcinoma, 2002

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined to the nasopharynx		
T2	Tumor extends to soft tissues		
T2a	Tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension		
T2b	Any tumor with parapharyngeal extension		
T3	Tumor involves bony structures and/or paranasal sinuses		
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa ^a		
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa ^a		
N3	Metastasis in lymph node(s) ^a >6 cm and/or to supraclavicular fossa		
N3a	Greater than 6 cm in dimension		
N3b	Extension to the supraclavicular fossa ^b		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping: nasopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
Stage IVA	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1-

^aMidline nodes are considered ipsilateral nodes.

^bSupraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (i) the superior margin of the sternal end of the clavicle, (ii) the superior margin of the lateral end of the clavicle, and (iii) the point where the neck meets the shoulder. Note that this would include caudal portions of Levels IV and V. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

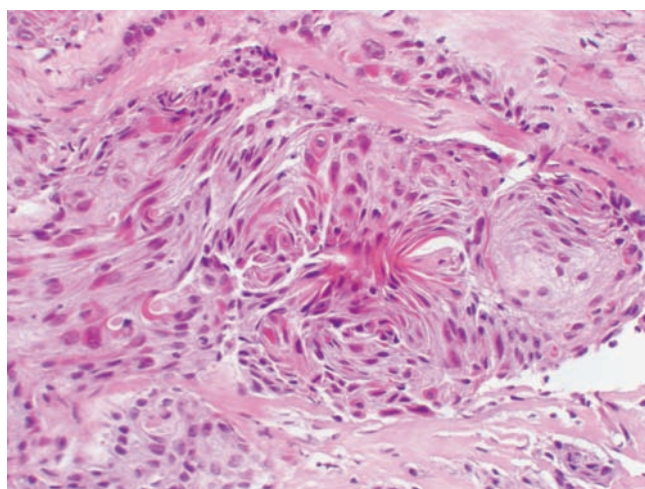
Abbreviation: AJCC: American Joint Committee on Cancer.

Source: From Ref. 54.

(Fig. 67). The cell margins are distinct and the junction between stroma and epithelium is sharp. This type has a strong relationship to EBV, tends to disseminate from its site of origin, and has a variable but usually good response to irradiation (60).

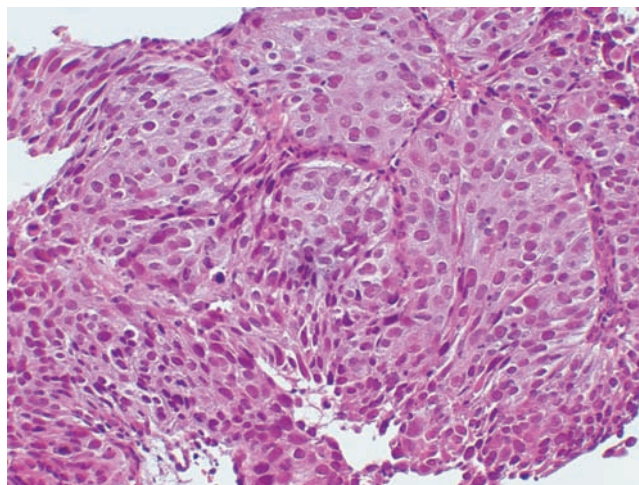
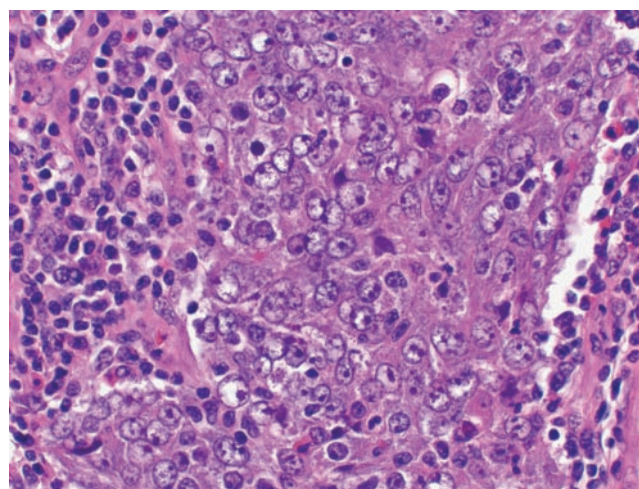
Table 32 Classification of Nasopharyngeal Carcinoma

World Health Organization (1978)
1. Squamous cell carcinoma
2. Nonkeratinizing carcinoma
3. Undifferentiated carcinoma
World Health Organization (1991)
1. Squamous cell carcinoma
2. Nonkeratinizing carcinoma
a. Differentiated nonkeratinizing carcinoma
b. Undifferentiated carcinoma
World Health Organization (2005)
1. Squamous cell carcinoma
2. Nonkeratinizing carcinoma
a. Differentiated nonkeratinizing carcinoma
b. Undifferentiated carcinoma
3. Basaloid squamous carcinoma

**Figure 66** Squamous cell carcinoma of the nasopharynx. Observe the dyskeratotic cells (H&E, 200 $\times$).

Undifferentiated carcinoma (WHO III) is composed of cells with indistinct margins and round to oval nuclei with prominent, round nucleoli (Fig. 68). The cells tend to grow in a syncytium rather than having a stratified or paved appearance. In some instances, the tumor grows in well-defined epithelial aggregates (Regaud pattern) easily recognizable as a carcinoma. In other instances, it grows as ill-defined sheets, small clusters, or individual cells admixed with lymphocytes (Schmincke pattern), simulating a malignant lymphoma (61–65). The lymphoid element, however, is not malignant and is rarely, if ever, observed in sites of metastasis. The lymphocytes are mainly T cells of CD8 subtype (66,67).

Undifferentiated carcinomas are often designated as lymphoepitheliomas. Occasionally, they may be associated with an exuberant infiltrate of eosinophils (25–35% of cases in endemic areas and especially the undifferentiated type) and masquerade as Hodgkin's disease or eosinophilic granuloma (68–70). The eosinophilia has no prognostic significance. A few cases may also contain epithelioid granulomas, which may

**Figure 67** Nonkeratinizing (differentiated nonkeratinizing) carcinoma of the nasopharynx. This variant resembles transitional cell carcinoma of the genitourinary tract. The nuclei are relatively uniform and, for the most part, are devoid of prominent nucleoli (H&E, 200 $\times$).**Figure 68** Undifferentiated carcinoma of the nasopharynx. The cells have a syncytial arrangement and contain large, vesicular nuclei with prominent nucleoli. Note the lymphocytes in the background that also extend between tumor cells (H&E, 400 $\times$).

be so prominent as to mask small islands of tumor cells (71). The undifferentiated carcinoma may also be mistaken for immunoblastic sarcoma. Immunoperoxidase stains for keratin, leukocyte common antigen, and immunoglobulins now allow one to distinguish between these entities with ease.

The undifferentiated carcinoma is the type most often found in children. It has a strong correlation with EBV, tends to disseminate, and has a good response to irradiation (60) (Fig. 69).

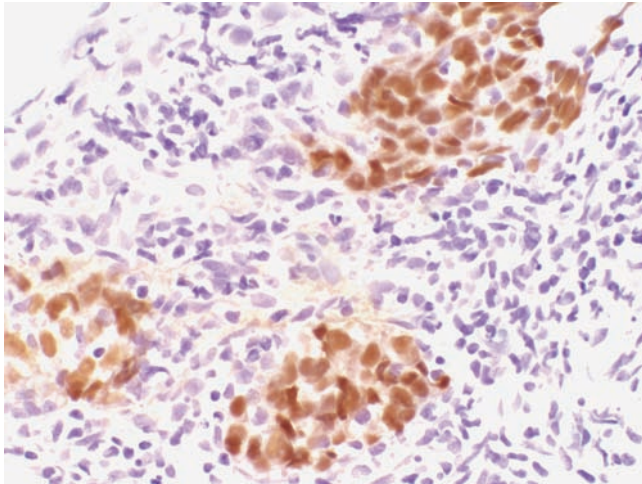


Figure 69 Positive EBER stain for Epstein-Barr virus in an undifferentiated nasopharyngeal carcinoma. *Abbreviation:* EBER, Epstein-Barr virus–encoded RNA.

It is generally agreed that the above three types of NPCs actually represent variants of squamous cell carcinoma. The histological distinction among these three tumor types is by no means always sharp. In fact, in the series of Shanmugaratnam et al., 26% of 363 NPCs had features of more than one of the above histological patterns (72). In such a case, the tumor is classified according to its dominant component.

NPC may also contain amyloid. Prathap et al. studied consecutive biopsies in 434 Malaysian patients with NPC and found amyloid in 12% of the tumors. The amyloid was present in all three histological types of NPC but was highest in nonkeratinizing carcinoma (NKC) (22%) followed by squamous cell carcinoma (12%) and undifferentiated carcinoma (7%). The amyloid was patchy in distribution and often localized to a small part of the tumor. No significance was apparent in patients with this finding (73).

Basaloid squamous carcinoma is distinctly unusual in the nasopharynx. Histologically, it is composed primarily of smooth contoured lobules of mitotically active basaloid cells with comedonecrosis and occasional peripheral palisading of nuclei. The squamous component is generally small and, at times, elusive due to surface ulceration. Three cases have been described in the nasopharynx in Hong Kong, and all three were associated with the EBV (74).

The frequency of the above histological types varies according to geographic location. In North America, about 75% of cases are of the nonkeratinizing type (WHO II and III) and 25% squamous cell carcinoma (60) (WHO I). In endemic areas, such as Hong Kong, almost all (99%) are of the nonkeratinizing type (WHO II and III). The frequency of basaloid squamous carcinoma in the nasopharynx is unknown, but appears to be distinctly uncommon (1).

F. Immunohistochemistry

NPCs are positive pankeratin, AE1/3 and p63. They are also positive for CK 5/6, 8, 13, and 19 and usually negative for CK7 and 20 (1,75). CAM 5.2 and epithelial membrane antigen are weak and patchy. The lymphoid cells are mixture of the T and B cells, with the former predominating (66,67). Plasma cells are polyclonal. Some tumors also contain scattered S-100 protein-positive dendritic cells, and the more of these cells seen, allegedly the better the prognosis (76,77).

G. Viral Studies

If one employs in situ hybridization or the polymerase chain reaction, EBV genomes can be detected in most NPCs, especially the nonkeratinizing variants (WHO II and III) (Fig. 69). The incidence of finding EBV in the squamous cell carcinoma variant of NPC, however, is controversial and, if found at all, is usually limited to a few scattered cells in the dysplastic surface epithelium or in the relatively “nonkeratinized” portion of the tumor and then only low copies of the virus are found (78–81).

According to Pathmanathan et al., EBV infection is an early initiating event in the development of NPC. They observed evidence of the virus in 11 cases of preinvasive lesions of the nasopharynx and that the EBV DNA was clonal, indicating that the preinvasive lesions arose from a single EBV-infected cell. Moreover, they noted that the EBV-induced clonal proliferation in these preinvasive lesions often progressed to an invasive carcinoma within one year (82). Pak et al., however, indicate that the interval from in situ to invasive NPC may take as long as four or five years (83).

Hording et al. studied 38 NPCs for the presence of the HPV. Four of 15 squamous carcinomas were positive for HPV (1 HPV-11 and 3 HPV-16). None of the remaining 23 undifferentiated and nonkeratinizing carcinomas harbored HPV. They suggested that the HPV might be responsible for some EBV-negative squamous cell carcinomas of the nasopharynx (15).

H. Molecular-Genetic Data

Cytogenetic studies of NPC have shown multiple chromosomal abnormalities, most of which are non-specific. The only somewhat consistent finding has been a loss of genetic material at two loci (3p 14 and 3p25) on the short arm of chromosome 3 in a series of 36 patients from China (84).

The frequency of chromosomal damage varies with the stage of the tumor; early-stage tumors (I and II) have fewer genetic changes than those observed in advanced stages (III and IV). Gains in genetic material have been observed, in decreasing order of frequency, on 12p, 1q, 17q, 11q, and 12q. Loss of genetic material has been observed at 3p, 9p, 11q, 13q, and 14q (1,85).

Whether DNA tumor ploidy has prognostic significance remains controversial. Costello et al. concluded that tumor ploidy was not a significant

Table 33 UNPC Vs. SNUC

Feature	UNPC	SNUC
Location	Nasopharynx	Sinonasal tract
Clinical	Small primary + cervical lymph nodes	Large primary, +/- cervical lymph nodes
Imaging	Little destruction or spread beyond site of origin	Marked destruction and spread beyond site of origin
Growth	Syncytial	Trabeculae, nests, sheets
Cells	Large, vesicular nuclei with prominent nucleoli	Hyperchromatic to vesicular nuclei with or without nucleoli
Mitoses	Not prominent	Very prominent
Necrosis	Not prominent	Very prominent
Vascular invasion	Not prominent	Very prominent
Lymphocytes	Heavy infiltrate	Absent to mild
EBV	+	—(in United States)
CK5/6 and 13	+	—

Abbreviations: UNPC, undifferentiated nasopharyngeal carcinoma; SNUC, sinonasal undifferentiated carcinoma.

determinant of prognosis, while Cheng et al. and Yip et al. observed that diploid tumors had a significant survival advantage over those that were aneuploid (86–88).

P53 overexpression has been reported in 31% to 95% of NPCs and, with few exceptions, does not appear to be a significant prognostic factor (89–91). In a study of 30 NPCs, Roychowdhury et al. noted that intense angiogenesis and C-erb B2 overexpression correlated with a tendency for distant metastasis and/or shorter overall survival (92). Shi et al. in a review of 87 NPCs found no association between tissue angiogenesis (microvessel density count) and clinical behavior (93).

In a review of 49 NPCs, Bar-Sela et al. observed that one-third were positive for C-Kit and none for C-erb B2 (HER2) (94). The C-Kit positive tumors were all EBV-positive and nonkeratinizing type (WHO II and III). Although the C-Kit-positive tumors tended to be associated with a slightly better prognosis, this was not statistically significant.

There is preliminary evidence to suggest that patients with tumors that are Bcl-2-negative and C-Myc-positive have a better prognosis (lower rates of recurrence and death from disease) compared with those whose tumors are Bcl-2 positive and c-Myc-negative (95,96).

I. Differential Diagnosis

The keratinizing NPC (squamous cell carcinoma, WHO I) is easily recognized and resembles squamous cell carcinoma anywhere else in the body. The non-keratinizing variants (WHO II and III), on the other hand, may be more problematic and can be confused with a myriad of other small round cell tumors of the sinonasal tract, including malignant lymphoma, malignant melanoma, ONB, extramedullary plasmacytoma, and rhabdomyosarcoma. SNUC, especially, is often confused with the undifferentiated NPC (WHO III). Features that are useful in separating these two neoplasms are shown in Table 33. The other small round cell tumors can usually be excluded with an appropriate panel of immunostains [leukocyte common antigen, S-100 protein, HMB-45, synaptophysin, immunoglobulin G (IgG), Lambda and kappa light chains, myogenin, etc.].

Primary LEC of the sinonasal tract should also be distinguished from the undifferentiated NPC. Since the two are identical histologically and both contain the EBV, separating the two depends on identifying the location of the tumor either in the sinonasal tract or nasopharynx (97) (Figs. 48 and 68).

Basaloid squamous carcinoma, in turn, is occasionally confused with adenoid cystic carcinoma. These two can be distinguished by features shown in Table 34.

J. Treatment and Prognosis

Because of the strategic location of the nasopharynx and the tendency for the tumor to invade surrounding tissues, the first line of therapy for NPC is irradiation (98–102). Surgery, if used at all, is reserved for radio-resistant and/or locally recurrent tumors (103–107). As the local and regional disease can be adequately managed by radiotherapy, the role of chemotherapy is usually reserved for disseminated disease and, more

Table 34 BSCC Vs. ACC

Feature	BSCC	ACC
Lymph nodes	+	—
Cribiform pattern	focal	often prominent
Nuclei	Hyperchromatic to vesicular, round	dark, angulated
Nucleoli	+/-	—
Mitoses	+	+/-
Squamous carcinoma	+	—
Perineural invasion	rare	frequent
Comedonecrosis	prominent	rare
Muscle specific actin	Neg. or focal	diffuse
Myoepithelial cells ^a	—	+
P53	+	—
Ki-67	high	low
S-100	focal, dendritic cells	diffuse
C-kit	+/-	+
P63	diffuse, basaloid, and squamous cells	myoepithelial cells only

^aAlthough in our experience myoepithelial cells are usually not seen in BSCC, a recent abstract indicates that myoepithelial cells may be seen in some BSCCs (36).

Abbreviations: BSCC, basaloid squamous cell carcinoma; ACC, adenoid cystic carcinoma.

recently, has also been used in a neoadjuvant setting (108–113). Newer therapeutic options are being explored, including brachytherapy, interferon gamma, immunization with EBV peptide-pulsed dendritic cells, and photodynamic therapy (114–116).

After treatment with radiation, it may take up to 10 weeks for the tumor to disappear histologically. If posttreatment biopsy is still positive for tumor after 10 weeks, additional salvage therapy is warranted (117,118).

Screening for LMP-1 also seems to be a valuable test to monitor therapy and early recurrence of NPC following radiotherapy. According to Tsang et al., LMP-1 becomes undetectable at a median interval of 4.3 weeks (range 1.3–28 weeks) after the beginning of irradiation. If LMP-1 reappears, the patient is at risk for recurrence. In their study, the median interval between the reappearance of LMP-1 and abnormal mucosal findings by endoscopy was 11.9 weeks (range 2.7–27.4 weeks) (119).

At times, it is often difficult to distinguish on biopsies radiation changes from recurrent NPC. If the LMP-1 is positive, then the biopsy most likely represents recurrent tumor rather than radiation-induced atypia-dysplasia.

Sixty percent to 85% of patients with NPCs will have positive cervical lymph nodes at the time of diagnosis, but less than 5% will demonstrate clinical evidence of distant metastasis (4,25,34). However, during the course of the disease, 20% to 60% (depending on whether clinical or autopsy data are used) will develop tumor dissemination below the clavicles, usually to the bones, distant lymph nodes, lungs, and liver (25,120–122). Ninety-eight percent of distant metastases are detected within three years of diagnosis (122). Their presence is an ominous sign of impending death. The median survival following their appearance is only six months (121). According to Vikram et al., the presence of distant metastases correlates with the N stage but not T stage (120). The incidence of distant metastasis in patients whose cervical lymph nodes measure less than 3 cm, 3 to 6 cm, and more than 6 cm is 10%, 25%, and 50%, respectively (123).

In a review of 103 patients with NPCs treated by radiation therapy, Bailet et al. observed the 5-, 10-, and 15-year overall survival rates were 58%, 47%, and 41%, respectively, with a median survival of 96 months (124). Local recurrences following radiation therapy continue to be a problem and range from approximately 30% to 45% (120,124,125). In general, the greater the T stage the more likely that the patient will develop local failure (125).

Keratinizing carcinomas (squamous cell carcinoma; WHO 1) have a much worse prognosis than nonkeratinizing carcinomas (nonkeratinizing carcinoma, WHO 2, undifferentiated carcinoma, WHO 3). The overall five-year survival rate for patients with NPCs in the United States is about 40% to 50%. For specific histological types, the five-year survival is 20% to 40% for squamous cell carcinoma (WHO 1) and about 65% for the nonkeratinizing carcinomas (WHO 2 and 3).

The status of the regional lymph nodes also affects prognosis. Lymph nodes confined to the upper neck, regardless of size, and whether they are unilateral or bilateral, fixed or nonfixed, do not carry the same weight as those present in the lower neck–supraclavicular area (25,126). Positive lymph nodes in the latter location are associated with a poor prognosis.

The prognosis for NPC is better in young patients (younger than 40 years) than old, and in females than in males. Cranial nerve involvement also adversely affects prognosis, whereas erosion of the base of the skull does not (127). Keratinizing histology and absence of EBV indicate a poor prognosis.

In contrast to other patients with mucosal head and neck squamous carcinomas who have an increased frequency for developing additional primary tumors (field effect of Slaughter), patients with NPCs do not exhibit an increased frequency of second primaries, probably related to different risk factors. Patients with NPCs, however, are at risk, though small, for developing radiation-induced neoplasms (128–130).

XXV. PAPILLARY ADENOCARCINOMA OF THE NASOPHARYNX

A. Introduction

The vast majority of malignant tumors of the nasopharynx are either keratinizing or nonkeratinizing squamous cell carcinomas or malignant lymphomas (1,2). Adenocarcinomas are uncommon, constituting no more than 6% of all malignancies, and, of these, most are derived from the mucoserous (minor salivary) glands and can be classified according to standard categories (adenoid cystic carcinoma, mucoepidermoid carcinoma (MEC), and such) (3). Exceptionally, adenocarcinomas may also arise from the mucosa and, when they do, they are typically papillary and are referred to as papillary adenocarcinomas of the nasopharynx (PACN) (4–6).

B. Clinical Features

PACNs are slightly more common in males (60%) and occur in individuals from 11 to 64 years of age (median 33 years) (4–6). Most present with airway obstruction. Other less common symptoms include serous otitis media, with or without hearing loss, and postnasal drip with blood-tinged sputum. Rarely, the tumor may be an incidental finding following adenoidectomy.

PACNs are typically confined to the nasopharynx and, on physical examination, present as exophytic or pedunculated masses, with a papillary, nodular, or cauliflower-like appearance. The tumors range from 0.3 to 4.0 cm, and most often they involve the roof, lateral or posterior walls of the nasopharynx.

There are no known risk factors associated with the development of this tumor. None of the patients

thus far has had a significant history of tobacco or alcohol abuse or occupational, environmental, or radiation exposure (4).

There has been one case reported in a 29-year-old female with Turner's syndrome (6). Karkos, et al. describe a 72 year-old man with an "aggressive papillary tumor (papillary adenocarcinoma, endolymphatic sac tumor)" of the right ear (7). Past history revealed that seven years previously that he had a papillary adenocarcinoma removed from the nasopharynx. The two tumors were stated to be histologically similar. Whether the tumor in the middle ear was a recurrence of the nasopharyngeal tumor or a second primary malignancy was uncertain.

C. Pathology

The tumors arise from the surface epithelium of the nasopharynx and may remain in situ or become invasive. They are characterized by papillary and glandular growth patterns (Fig. 70). The papillae have fibrovascular cores and often show arborization, whereas the glands frequently have a back-to-back, often cribriform arrangement. Both papillae and glands are covered or lined by one or more layers of cuboidal to columnar cells, with pink cytoplasm and round to oval nuclei that vary from hyperchromatic to optically clear (Fig. 71). Mild to moderate nuclear pleomorphism may be seen, but nucleoli, mitoses, and necrosis are uncommon. A few tumors may also contain psammoma bodies. Vascular, lymphatic, or neural invasion are usually not seen.

PACNs typically contain periodic acid-Schiff, diastase-resistant intracytoplasmic granules, and stain focally positive for intracellular or luminal mucin (4).

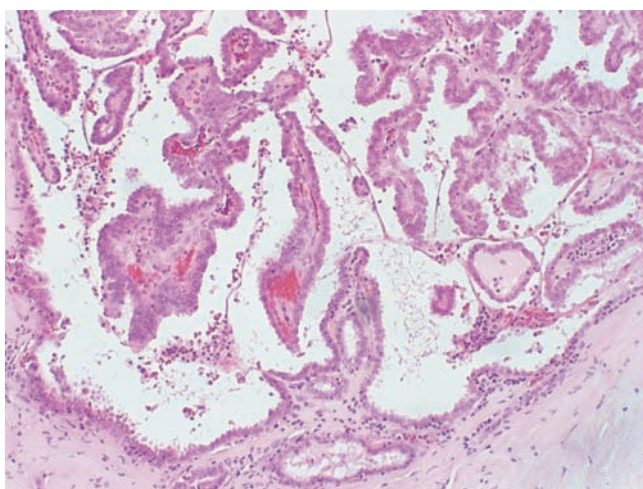


Figure 70 Papillary adenocarcinoma of the nasopharynx. Note the extensive branching and that the tumor is arising from the mucosa (H&E, 40 $\times$).

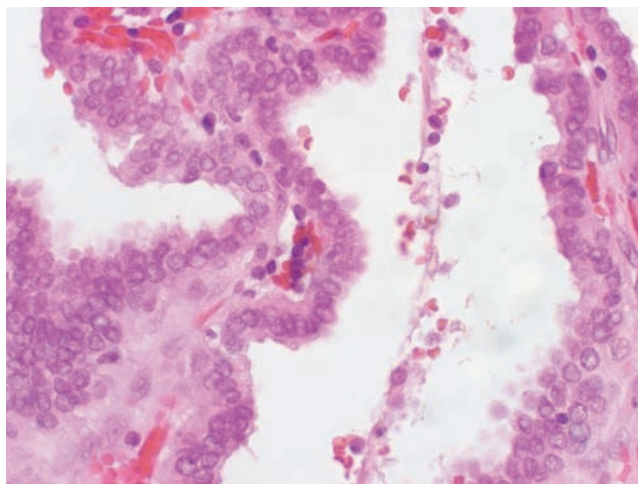


Figure 71 Papillary adenocarcinoma of the nasopharynx. The cells lining the papillae are often stratified and have nuclei that vary from hyperchromatic to optically clear (H&E, 400 $\times$).

D. Immunohistochemistry

PACNs are positive for pankeratin, epithelial membrane antigen, and CK7 and negative for CK20, CDX2, villin, glial fibrillary acidic protein, and S-100 protein (4,8,9). They may also focally stain for carcinoembryonic antigen.

Carrizo and Luna have described two cases that were positive for thyroid transcription factor-1 and positive for CK7 and 19 (10). The tumors are otherwise negative for thyroglobulin and have no association with the EBV (4).

E. Differential Diagnosis

The differential diagnosis includes papillary thyroid carcinoma, papillary variant of intestinal-type adenocarcinoma (P-ITAC), and low-grade papillary adenocarcinoma of salivary gland origin (LGPASO).

Because of the papillae and the occasional presence of psammoma bodies and optically clear nuclei, PACN can easily be mistaken for metastatic papillary thyroid carcinoma. Although a few are positive for thyroid transcription factor-1, they are negative for thyroglobulin and will typically show dysplasia or in situ changes of the surface epithelium (4,10).

P-ITAC, in contrast with PACN, occurs primarily in the nasal cavity and paranasal sinuses and is often (not invariably) associated with an occupation exposure to wood dust (11,12). P-ITAC also tends to be less glandular and more papillary. Rather than cuboidal cells, the papillae are covered by tall columnar and goblet cells, the latter of which are sparse to absent in PACN. P-ITAC may also contain Paneth cells and scattered endocrine cells that may express somatostatin, gastrin, serotonin, or other secretory substances on appropriate staining. Such cells are

not seen in PACN. P-ITAC also tends to be associated with a hemorrhagic, inflammatory background and often recurs following therapy. PACN, in contrast, has a “clean” background and rarely recurs.

Immunohistochemistry is also helpful. P-ITAC is typically CK7⁺, CK20⁺, CDX2⁺, villin⁺, while PACN is CK7⁺, CK20⁻, CDX2⁻, villin⁻.

LGPASO occurs almost exclusively in the oral cavity, especially the palate (13–15). Furthermore, it arises submucosally from minor salivary glands, rather than from the surface, as does the PACN. Staining for S-100 protein may also be helpful. Thus far, PACNs have been S-100 protein-negative, while LGPASOs are usually positive (4,15). LGPASOs are also more aggressive, with frequent local recurrence (27%) and, at times, lymph node metastasis (17%) (15).

F. Treatment and Prognosis

PACN is a slow-growing, indolent neoplasm that may recur but thus far has not metastasized to either cervical lymph nodes or more distant sites [with the possible case of Karkos et al. as noted above (7)]. The treatment of choice is surgery. Wenig et al. describe one case that was treated initially with full-course radiotherapy (4). The tumor recurred within months following treatment. The patient subsequently underwent surgical excision and was reported free of disease 11 years later. This singular experience casts doubts on the efficacy of radiation therapy. Photodynamic therapy has also been successful for an incompletely resected PACN (16).

XXVI. METASTASES TO THE NASAL CAVITY AND PARANSAL SINUSES

A. Introduction

Metastases to the nasal cavity and paranasal sinuses are rare and are hematogenously derived. Kent and Majumdar identified only two metastatic tumors of the maxillary sinuses in their review of 250 malignant sinonasal tumors on file at their regional medical center (1). In 2001, only 169 cases were recorded in the world literature (2).

The distribution of tumor among the sinuses and the most frequent tumors to metastasize to these sites are shown in Tables 35 and 36, respectively. In 10% to 15% of cases, the metastases are limited to the nasal cavity.

Table 35 Distribution of 168 Tumors Metastatic to Paranasal Sinuses

Sinus	Frequency
Maxillary	33%
Sphenoid	22%
Ethmoid	14%
Frontal	9%
Multiple sinuses	22%

Source: From Ref. 2.

Table 36 Most Frequent Sites of Tumors to Metastasize to the Paranasal Sinuses

Primary tumor	Frequency
Kidney	40%
Lung	9%
Breast	8%
Thyroid	8%
Prostate	7%
Miscellaneous	28%

Source: From Ref. 2.

B. Clinical Features

Metastases may occur in any age group. In a review of 82 cases, Bernstein et al. observed the median age at the time of diagnosis of the metastatic tumor to be 57 years (range 3 months–76 years) and that 60% of the patients were males (3).

Metastases to the sinonasal tract may be solitary or multifocal and ordinarily produce symptoms indistinguishable from those of a primary tumor. Among these are included nasal obstruction, headache, facial pain, visual disturbances, exophthalmos, facial swelling, cranial nerve deficits, and epistaxis (especially metastatic renal and thyroid carcinomas). In some instances, the metastasis may be the first manifestation of an otherwise clinically occult carcinoma.

C. Prognosis

Although the eventual outcome is usually poor, prognosis depends, in part, on whether the sinonasal metastasis is isolated or part of widespread disseminated disease. If the metastasis to the nasal cavity and sinuses is localized and treated aggressively, Kent and Majumdar indicated that the average survival following discovery of the metastasis may be as long as 20 to 30 months (1).

REFERENCES

I. RHINOSINUSITIS (SINUSITIS, RHINITIS)

1. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997; 117:S1–S7(Suppl Number 3, part 2).
2. Kennedy DW, Gwaltney JM Jr, Jones DW. Medical management of sinusitis: Educational goals and management guidelines. *The International Conference on Sinus Disease. Ann Otol Rhinol Laryngol Suppl* 1995; 167:22–30.
3. Clayman GL, Adams GL, Paugh DR, et al. Intracranial complications of paranasal sinusitis: a combined institutional review. *Laryngoscope* 1991; 101:234–239.
4. Tovi F, Benharroch D, Gatot A, et al. Osteoblastic osteitis of maxillary sinus. *Laryngoscope* 1992; 102:426–430.
5. Chiu AG. Osteitis in chronic rhinosinusitis. *Otolaryngol Clin North Am* 2005; 30:1237–1242.
6. Engler DB, Grant JA. Allergic rhinitis: a practical approach. *Hosp Pract (Off Ed)* 1991; 26:105–112.
7. Naclerio RM. Allergic rhinitis. *N Engl J Med* 1991; 325: 860–869.

8. Plaut M, Valentine MD. Allergic rhinitis. *New Engl J Med* 2005; 353:1934–1944.
9. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997; 99:5781–5786.
10. Lieberman P. Rhinitis—allergic and nonallergic. *Hosp Pract (Off Ed)* 1988; 23:117–132.
11. Mygind N. Pathogenesis of allergic rhinitis. *Acta Otolaryngol Suppl (Stockh)* 1979; 360:9–12.
12. Haberal I, Corey JP. The role of leukotrienes in nasal allergy. *Otolaryngol Head Neck Surg* 2003; 129:274–279.
13. Mabry RL. Allergic rhinosinusitis. In: Bailey BJ, Johnson JT, Kohut RI, et al. ed. *Head Neck Surgery—Otolaryngology*. Philadelphia: JB Lippincott, 1993:290–301.
14. Whiteside TL, Rabin BS, Zetterberg J, et al. The presence of IgE on the surface of lymphocytes in nasal polyps. *J Allergy Clin Immunol* 1975; 55:186–194.
15. Shatkin JS, Delsupehe KG, Thisted RA, et al. Mucosal allergy in the absence of systemic allergy in nasal polyposis and rhinitis: a meta-analysis. *Otolaryngol Head Neck Surg* 1994; 111:553–556.
16. Postic WP, Wetmore RF. Pediatric rhinology. In: Goldman JL, ed. *The Principles and Practice of Rhinology*. New York: John Wiley and Sons, 1987:801–845.
17. Piccirillo JF. Acute bacterial sinusitis. *N Engl J Med* 2004; 351:902–910.
18. Evans FO, Sydnor JB, Moore WEG, et al. Sinusitis of the maxillary antrum. *N Engl J Med* 1976; 293:735–739.
19. Frederick J, Braude A. Anaerobic infection of the paranasal sinuses. *N Engl J Med* 1974; 290:135–137.
20. Kimmelman CP, Ali GHA. Vasomotor rhinitis. *Otolaryngol Clin North Am* 1986; 19:65–71.
21. Kopke RD, Jackson RL. Rhinitis. In: Baily BJ, Johnson JT, Kohut RI, et al. ed. *Head and Neck Surgery—Otolaryngology*. Philadelphia: JB Lippincott, 1993:269–289.
22. Pogorel E. Vasomotor rhinitis and nasal dyspnea. *Ear Nose Throat J* 1977; 56:261–272.
23. Blom HM, Godthelp T, Fokkens WJ, et al. Mast cells, eosinophils and IgE—positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. *Eur Arch Otorhinolaryngol* 1995; 252(suppl 1): 533–539.
24. Al-Samarrae SM. Treatment of “vasomotor rhinitis” by local application of silver nitrate. *J Laryngol Otol* 1991; 105:285–287.
25. Golding-Wood PH. Vidian neurectomy: its results and complications. *Laryngoscope* 1973; 83:1673–1683.
26. Han-Sen C. The ozena problem. Clinical analysis of atrophic rhinitis in 100 cases. *Acta Otolaryngol* 1982; 93:461–464.
27. Shehata MA. Atrophic rhinitis. *Am J Otolaryngol* 1996; 17:81–86.
28. El-Barbary AE-S, Yassin A, Fouad H, et al. Histo-pathological and histochemical studies in atrophic rhinitis. *J Laryngol Otol* 1976; 84:1103–1112.
29. Sinha SN, Sardana DS, Rajvanshi VS. A nine year review of 273 cases of atrophic rhinitis and its management. *J Laryngol Otol* 1977; 91:591–600.
30. Dudley JP. Atrophic rhinitis: antibiotic treatment. *Am J Otolaryngol* 1987; 8:387–390.
31. Samter M, Beers RF Jr. Concerning the nature of intolerance to aspirin. *J Allergy* 1967; 40:281–293.
32. Samter M. Intolerance to aspirin. *Hosp Pract (Off Ed)* 1973; 8:85–90.
33. Zeitz HJ. Bronchial asthma, nasal polyps, and aspirin sensitivity: Samter’s syndrome. *Clin Chest Med* 1988; 9:567–576.
34. Probst L, Stoney P, Jeney E, et al. Nasal polyps, bronchial asthma and aspirin sensitivity. *J Otolaryngol* 1992; 21: 60–65.
35. Moloney JR. Nasal polyps, nasal polypectomy, asthma and aspirin sensitivity. Their association in 445 cases of nasal polyps. *J Laryngol Otol* 1977; 91:837–846.
36. McFadden EA, Kany RJ, Fink JN, et al. Surgery for sinusitis and aspirin triad. *Laryngoscope* 1990; 100:1043–1046.
37. Patriarca G, Romano A, Schiavino D, et al. ASA disease: the clinical relationship of nasal polyposis to ASA intolerance. *Arch Otorhinolaryngol* 1986; 243:16–19.
38. Settigane GA. Nasal polyps: epidemiology, pathology, immunology, and treatment. *Am J Rhinol* 1987; 1:119–126.
39. Ogino S, Harada T, Okawachi, et al. Aspirin-induced asthma and nasal polyps. *Acta Otolaryngol Suppl (Stockh)* 1986; 430:21–27.
40. English GM, Spector S, Farr R, et al. Histopathology and immunofluorescent immunoglobulin in asthmatics with aspirin idiosyncrasy. *Arch Otolaryngol Head Neck Surg* 1987; 113:377–379.
41. Gosepath J, Mann WJ. Current concepts in therapy of chronic rhinosinusitis and nasal polyposis. *ORL* 2005; 67:125–136.
42. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome). Clinical and immunologic presentation. *J Allergy Clin Immunol* 1981; 67:253–262.
43. Moneret-Vautrin, Hsieh V, Wayoff M, et al. Nonallergic rhinitis with eosinophilia syndrome. A precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. *Ann Allergy* 1990; 64:513–518.
44. Toohill RJ, Lehman RH, Grossman TW, et al. Rhinitis medicamentosa. *Laryngoscope* 1981; 91:1614–1621.
45. Mabry RL. Rhinitis medicamentosa: the forgotten factor in nasal obstruction. *South Med J* 1982; 75:817–819.
46. Graf P, Hallen H, Juto J-E. The pathophysiology and treatment of rhinitis medicamentosa. *Clin Otolaryngol* 1995; 20:224–229.
47. Schatz M, Zeiger RS. Diagnosis and management of rhinitis during pregnancy. *Allergy Proc* 1988; 9:545–554.
48. Welch AR, Birchall JP, Stafford FW. Occupational rhinitis—possible mechanisms of pathogenesis. *J Laryngol Otol* 1995; 109:104–107.
49. Holt GR. Effects of air pollution on the upper aerodigestive tract. *Otolaryngol Head Neck Surg* 1996; 114:201–204.
50. Trevino RJ. Air pollution and its effect on the upper respiratory tract and allergic rhinosinusitis. *Otolaryngol Head Neck Surg* 1996; 114:239–241.
51. Sala E, Hytonen M, Tupasela O, et al. Occupational laryngitis with immediate allergic or immediate type specific chemical hypersensitivity. *Clin Otolaryngol* 1996; 21:42–48.
52. Torjussen W. Rhinoscopic findings in nickel workers, with special emphasis on the influence of nickel exposure and smoking habits. *Acta Otolaryngol* 1979; 88:279–288.
53. Camilleri AE. Chronic sinusitis and yellow nail syndrome. *J Laryngol Otol* 1990; 104:811–813.
54. Varney VA, Cumerworth V, Sudderick R, et al. Rhinitis, sinusitis and the yellow nail syndrome: a review of symptoms and response to treatment in 17 patients. *Clin Otolaryngol* 1994; 19:237–240.
55. Smith MP. Dysfunction of carbohydrate metabolism as an element in the set of factors resulting in the polysaccharide nose and nasal polyps (the polysaccharide nose). *Laryngoscope* 1971; 81:636–644.
56. Smith MP, Frable WJ. Ultrastructure of the polysaccharide nose: its relationship to allergy and carbohydrate dysfunction. *Laryngoscope* 1973; 83:783–795.

II. NASAL POLYPS

- Bateman ND, Fahy C, Woolford TJ. Nasal polyps: still more questions than answers. *J Laryngol Otol* 2003; 117:1-9.
- Pawliczak R, Lewandowska-Polak A, Kowalski ML. Pathogenesis of nasal polyps: an update. *Curr Allergy Asthma Rep* 2005; 5:463-471.
- Bernstein JM. Update on the molecular biology of nasal polyposis. *Otolaryngol Clin North Am* 2005; 38:1234-1255.
- Larsen PL, Tos M. Origin of nasal polyps. *Laryngoscope* 1991; 101:305-312.
- Andrews AE, Bryson JM, Rowe-Jones JM. Site of origin of nasal polyps: relevance to pathogenesis and management. *Rhinology* 2005; 43:180-184.
- Sorensen H, Mygind N, Tygstrup I, et al. Histology of nasal polyps of different etiology. *Rhinology* 1977; 15:121-128.
- Baumgarten C, Kunkel G, Rudolf R, et al. Histopathological examinations of nasal polyps of different etiology. *Arch Otorhinolaryngol* 1980; 226:187-197.
- Kakoi H, Hiraide F. A histological study of formation and growth of nasal polyps. *Acta Otolaryngol* 1987; 103:137-144.
- Krajina Z, Zirdum A. Histochemical analysis of nasal polyps. *Acta Otolaryngol* 1987; 103:435-440.
- Settipane GA. Nasal polyps: epidemiology, pathology, immunology and treatment. *Am J Rhinol* 1987; 1:119-126.
- Petruson B, Hansson H-A, Petruson K. Insulin-like growth factor I is a possible pathogenic mechanism in nasal polyps. *Acta Otolaryngol* 1988; 106:156-160.
- Perkins JA, Blakeslee DB, Andrade P. Nasal polyps: a manifestation of allergy? *Otolaryngol Head Neck Surg* 1989; 101:641-645.
- Tos M. The pathogenic theories on formation of nasal polyps. *Am J Rhinol* 1990; 4:51-56.
- Larsen PL, Tos M, Kuijpers W, et al. The early stages of polyp formation. *Laryngoscope* 1992; 102:670-677.
- Otsuka H, Ohkubo K, Seki H, et al. Mast cell quantitation in nasal polyps, sinus mucosa and nasal turbinate mucosa. *J Laryngol Otol* 1993; 107:418-422.
- Norlander T, Fukami M, Westrin KM, et al. Formation of mucosal polyps in the nasal and maxillary sinus cavities by infection. *Otolaryngol Head Neck Surg* 1993; 109:522-529.
- Ogino S, Abe Y, Irifune M, et al. Histamine metabolism in nasal polyps. *Ann Otol Rhinol Laryngol* 1993; 102:152-156.
- Hosemann W, Gode U, Wagner W. Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery. *Am J Otolaryngol* 1994; 15:85-89.
- Berstein JM, Gorfien J, Noble B. Role of allergy in nasal polyposis: a review. *Otolaryngol Head Neck Surg* 1995; 113:724-732.
- Coste A, Rateau J-G, Roudot-Thoraval F, et al. Increased epithelial cell proliferation in nasal polyps. *Arch Otolaryngol Head Neck Surg* 1996; 122:432-436.
- Busuttil A, Chandrachud H, Kerr AIG, et al. Simple nasal polyps and allergic manifestations. *J Laryngol Otol* 1978; 92:477-488.
- Maloney JR. Nasal polyps, nasal polypectomy, asthma and aspirin sensitivity. Their association in 445 cases of nasal polyps. *J Laryngol Otol* 1977; 91:837-846.
- Schramm VL Jr, Effron MZ. Nasal polyps in children. *Laryngoscope* 1980; 90:1488-1495.
- Kaufman LM, Folk ER, Chow JM. Invasive sinonasal polyps causing ophthalmoplegia, exophthalmos, and visual field loss. *Ophthalmology* 1989; 96:1667-1672.
- Arab M, Friedman M, Weingarten J. Nasal polyposis with invasion into the orbit. *Arch Otolaryngol* 1983; 109:273-274.
- Rejowski JE, Caldarelli DD, Campanella RS, et al. Nasal polyps causing bone destruction and blindness. *Otolaryngol Head Neck Surg* 1982; 90:505-506.
- Donovan R, Johansson SGO, Bennich H, et al. Immunoglobulins in nasal polyp fluid. *Int Arch Allergy Appl Immunol* 1970; 37:154-166.
- Whiteside TL, Rabin BS, Zetterberg, et al. The presence of IgE on the surface of lymphocytes in nasal polyps. *J Allergy Clin Immunol* 1975; 55:186-194.
- Alun-Jones T, Hill J, Leighton SEJ, et al. Is routine histologic examination of nasal polyps justified? *Clin Otolaryngol* 1990; 15:217-219.
- Kale SU, Mohite U, Rowlands D, et al. Clinical and histopathological correlation of nasal polyps: are there any surprises? *Clin Otolaryngol* 2001; 26:321-323.
- Garavello W, Gaini RM. Incidence of inverted papilloma in recurrent nasal polyposis. *Laryngoscope* 2006; 116:221-223.
- Compagno J, Hyams VJ, Lepore ML. Nasal polyps with stromal atypia. Review and follow-up study of 14 cases. *Arch Pathol Lab Med* 1976; 100:224-226.
- Klenoff BH, Goodman ML. Mesenchymal cell atypicality in inflammatory polyps. *J Laryngol Otol* 1977; 91:751-756.
- Kindblom L-G, Angervall L. Nasal polyps with atypical stroma cells: a pseudosarcomatous lesion. *Acta Pathol Microbiol Immunol Scand Sect A* 1984; 92:65-72.
- Nakayama M, Wenig BM, Heffner DK. Atypical stromal cells in inflammatory nasal polyps: immunohistochemical and ultrastructural analysis in defining histogenesis. *Laryngoscope* 1995; 105:127-134.
- de la Cruz Mera A, Lopez MJS, Royo EM, et al. Premalignant changes in nasal and sinus polyps: a retrospective 10 year study (1979-1988). *J Laryngol Otol* 1990; 104:210-212.
- Hasegawa M, Nasu M, Ohki M, et al. Malignant transformation of nasal polyp. Case report. *Arch Otolaryngol Head Neck Surg* 1988; 114:336-337.
- Westra WH, Holmes GF, Eisele DW. Bizarre epithelial atypia of the sinonasal tract after chemotherapy. *Am J Surg Pathol* 2001; 25:652-656.
- Busuttil A. Granulomas in nasal polyps. *J Laryngol Otol* 1975; 89:1087-1094.
- Wolff M. Granulomas in nasal mucous membranes following local steroid injections. *Am J Clin Pathol* 1974; 62:775-782.
- Coup AJ, Hopper IP. Granulomatous lesions in nasal biopsies. *Histopathology* 1980; 4:293-308.

III. ANTROCHOANAL POLYPS

- Killian G. The origin of choanal polypi. *Lancet* 1906; 2:81-82.
- Heck WE, Hallberg O, Williams HL. Antrochoanal polyp. *Arch Otolaryngol* 1950; 52:538-548.
- Hardy G. The choanal polyp. *Ann Otol Rhinol Laryngol* 1957; 66:306-326.
- Cook PR, Davis WE, McDonald R, et al. Antrochoanal polyposis. A review of 33 cases. *ENT J* 1993; 72:401-410.
- Min Y-G, Chung JW, Shin J-S, et al. Histologic structure of antrochoanal polyps. *Acta Otolaryngol* 1995; 115:543-547.
- Orvidas LJ, Beatty CW, Weaver AL. Antrochoanal polyps in children. *Am J Rhinol* 2001; 15:321-325.
- Sirola R. Choanal polyps. *Acta Otolaryngol* 1966; 61:42-48.
- Aktas D, Yetiser S, Gerek M, et al. Antrochoanal polyps: analysis of 16 cases. *Rhinology* 1998; 36:81-85.
- Chen JM, Schloss MD, Azouz ME. Antro-choanal polyp: a 10-year retrospective study in the pediatric population with a review of the literature. *J Otolaryngol* 1989; 18:168-172.

10. Schramm VL Jr, Effron MZ. Nasal polyps in children. *Laryngoscope* 1980; 90:1488-1495.
11. Myatt HM, Cabrera M. Bilateral antrochoanal polyps in a child: a case report. *J Laryngol Otol* 1996; 110:272-274.
12. Basu SK, Bandyopadhyay SN, Bora H. Bilateral antrochoanal polyps. *J Laryngol Otol* 2001; 115:561-562.
13. Towbin R, Dunbar JS, Bove K. Antrochoanal polyps. *AJR Am J Roentgenol* 1979; 132:27-31.
14. Smith CJ, Echevarria R, McLelland CA. Pseudosarcomatous changes in antrochoanal polyps. *Arch Otolaryngol* 1974; 99: 228-230.
15. Batsakis JG, Sneige N. Choanal and angiomatous polyps of the sinonasal tract. *Ann Otol Rhinol Laryngol* 1992; 101:623-625.
16. Yfantis HG, Drachenberg CB, Gray W, et al. Angiectatic nasal polyps that clinically simulate a malignant process. Report of 2 cases and review of the literature. *Arch Pathol Lab Med* 2000; 124:406-410.

IV. PRIMARY CILIARY DYSKINESIA (IMMOTILE CILIA SYNDROME)

1. Afzelius BA. Disorders of ciliary motion. *Hosp Pract (Off Ed)* 1986; 21:73-80.
2. Afzelius BA. Cilia-related diseases. *J Pathol* 2004; 204: 470-477.
3. Eliasson R, Mossberg B, Camner P, et al. The immotile-cilia syndrome. A congenital ciliary abnormality as an etiologic factor in chronic airway infection and male sterility. *N Engl J Med* 1977; 297:1-6.
4. Eavey RD, Nadol JB Jr, Holmes LB, et al. Kartagener's syndrome. A blinded, controlled study of cilia ultrastructure. *Arch Otolaryngol Head Neck Surg* 1986; 112:646-650.
5. Van Der Baan S, Veerman AJP, Bezemer PD, et al. Primary ciliary dyskinesia: Quantitative investigation of the ciliary ultrastructure with statistical analysis. *Ann Otol Rhinol Laryngol* 1987; 96:264-272.
6. Smallman LA. Primary ciliary dyskinesia and Young's syndrome. *Clin Otolaryngol* 1989; 14:271-278.
7. Boat TF, Carson JL. Ciliary dysmorphology and dysfunction—primary or acquired. *N Engl J Med* 1990; 323:1700-1702.
8. Ahmad I, Drake-Lee A. Nasal ciliary studies in children with chronic respiratory tract symptoms. *Rhinology* 2003; 41:69-71.
9. Chilvers MA, Rutman A, O'Callaghan C. Ciliary beat pattern is associated with specific ultrastructural defects in primary ciliary dyskinesia. *J Allergy Clin Immunol* 2003; 112:518-524.
10. Carson JL, Collier AM, Hu S-CS. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. *N Engl J Med* 1985; 312:463-468.
11. Rautanen M, Nuutinen J, Kiukaaniemi H, et al. Ultrastructural changes in human nasal cilia caused by the common cold and recovery of ciliated epithelium. *Ann Otol Rhinol Laryngol* 1992; 101:982-987.
12. Afzelius BA. Immotile cilia syndrome: past, present, and prospects for the future. *Thorax* 1998; 53:894-897.
13. Berdon WE, Ulrich W. Situs inversus, bronchiectasis, and sinusitis and its relation to immotile cilia: history of the disease and their discoveries—Manes Kartagener and Björn Afzelius. *Pediatr Radiol* 2004; 34:38-42.
14. Bent JP III, Smith RJH. Intraoperative diagnosis of primary ciliary dyskinesia. *Otolaryngol Head Neck Surg* 1997; 116:64-67.

V. CYSTIC FIBROSIS

1. Fanconi G, Wehlinger E, Knauer C. Das coeliakie-syndrom be: bronchiectasien. *Wien Med Wochenschr* 1936; 86:753-756.
2. Anderson D. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. *Am J Dis Child* 1938; 56:344-399.
3. Drake-Lee AB, Morgan DW. Nasal polyps and sinusitis in children with cystic fibrosis. *J Laryngol Otol* 1989; 103: 753-755.
4. Collins FS, Riordan JR, Tsui L-C. The cystic fibrosis gene: isolation and significance. *Hosp Pract (Off Ed)* 1990; 25: 47-57.
5. Collins FS. Cystic fibrosis: molecular biology and therapeutic implications. *Science* 1992; 256:774-779.
6. Davis PB. Cystic fibrosis: new perceptions, new strategies. *Hosp Pract (Ed)* 1992; 27:79-118.
7. Neglia JP, Fitzsimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. *N Engl J Med* 1995; 332:494-499.
8. Marx JL. The cystic fibrosis gene is found. *Science* 1989; 245:923-925.
9. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med* 2005; 352:1992-2001.
10. Keren E, Corey M, Kerem B-S, et al. The relationship between genotype and phenotype in cystic fibrosis—analysis of the most common mutation ($\Delta F508$). *N Engl J Med* 1990; 323:1517-1522.
11. Lewis MJ, Lewis EH III, Amos JA, et al. Cystic fibrosis. *Am J Clin Pathol* 2003; 120(suppl 1):S3-S13.
12. Tos M, Mogensen C, Thomsen J. Nasal polyps in cystic fibrosis. *J Laryngol Otol* 1977; 91:827-835.
13. Cepero R, Smith RJH, Catlin FI, et al. Cystic fibrosis—An otolaryngologic perspective. *Otolaryngol Head Neck Surg* 1987; 97:356-360.
14. Crockett DM, McGill TJ, Healey GB, et al. Nasal and paranasal sinus surgery in children with cystic fibrosis. *Ann Otol Rhinol Laryngol* 1987; 96:367-372.
15. Brihaye P, Clement PAR, Dab I, et al. Pathological changes of the lateral nasal wall in patients with cystic fibrosis (mucoviscidosis). In *J Pediatr Otorhinolaryngol* 1994; 141-147.
16. Davidson TM, Murphy C, Mitchell M, et al. Management of chronic sinusitis in cystic fibrosis. *Laryngoscope* 1995; 105:354-358.
17. Hui Y, Gaffnery R, Crysdale WS. Sinusitis in patients with cystic fibrosis. *Eur Arch Otorhinolaryngol* 1995; 252: 191-196.
18. Halvorson DJ. Cystic fibrosis: an update for the otolaryngologists. *Otolaryngol Head Neck Surg* 1999; 120:502-506.
19. Todd NW, Martin WS. Temporal bone pneumatization in cystic fibrosis patients. *Laryngoscope* 1988; 98: 1046-1049.
20. Haddad J Jr, Gonzalez C, Kurland G, et al. Ear disease in children with cystic fibrosis. *Arch Otolaryngol Head Neck Surg* 1994; 120:491-493.
21. Settipane GA. Nasal polyps: epidemiology, pathology, immunology and treatment. *Am J Rhinol* 1987; 1:119-126.
22. Hadfield PJ, Rowe-Jones JM, Makay IS. The prevalence of nasal polyps in adults with cystic fibrosis. *Clin Otolaryngol* 2000; 25:19-22.
23. Schramm VL Jr, Effron MZ. Nasal polyps in children. *Laryngoscope* 1980; 90:1488-1495.
24. Stern RC. The diagnosis of cystic fibrosis. *N Engl J Med* 1997; 336:487-491.

25. Grody WW. Cystic fibrosis. Molecular diagnosis, population screening and public policy. *Arch Pathol Lab Med* 1999; 123:1041-1046.
26. Oppenheimer EH, Rosenstein BJ. Differential pathology of nasal polyps in cystic fibrosis and atopy. *Lab Invest* 1979; 40:449-455.
27. Rulor JT, Brown HA, Logan GB. Nasal polyps and cystic fibrosis of the pancreas. *Arch Otolaryngol* 1963; 78:192-199.

VI. ALLERGIC MUCUS—ALLERGIC FUNGAL RHINOSINUSITIS

1. Katzenstein A-L, Sale SR, Greenberger PA. Pathologic findings in allergic aspergillus sinusitis. A newly recognized form of sinusitis. *Am J Surg Pathol* 1983; 7:439-443.
2. Ence BK, Gourley DS, Jorgensen NL, et al. Allergic fungal sinusitis. *Am J Rhinol* 1990; 4:169-178.
3. Cody DT II, Neel HB III, Ferreiro JA, et al. Allergic fungal sinusitis: the Mayo Clinic experience. *Laryngoscope* 1994; 104:1074-1079.
4. Lara JF, Gomez JD. Allergic mucin with and without fungus. A comparative clinicopathologic analysis. *Arch Pathol Lab Med* 2001; 125:1442-1447.
5. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. *Laryngoscope* 2001; 111:1006-1019.
6. Saferstein B. Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. *Chest* 1976; 70:788-790.
7. Miller JW, Johnston A, Lamb D. Allergic aspergillosis of the maxillary sinuses [abstr]. *Thorax* 1981; 36:710.
8. Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1994; 111:580-588.
9. Corey J, Romberger CF, Shaw GY. Fungal diseases of the sinuses. *Otolaryngol Head Neck Surg* 1990; 103:1012-1015.
10. Friedman GC, Hartwick W, Ro JY, et al. Allergic fungal sinusitis. Report of three cases associated with dematiaceous fungi. *Am J Clin Pathol* 1991; 96:368-372.
11. Allphin AL, Strauss M, Abdul-Karim FW. Allergic fungal sinusitis: problems in diagnosis and treatment. *Laryngoscope* 1991; 101:815-820.
12. Corey J, Delsupehe KG, Ferguson BJ. Allergic fungal sinusitis: allergic, infectious, or both? *Otolaryngol Head Neck Surg* 1995; 113:110-119.
13. Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathologic entity. *Laryngoscope* 2000; 110:799-813.
14. Sok JC, Ferguson BJ. Differential diagnosis of eosinophilic chronic rhinosinusitis. *Current Allergy Asthma Reports* 2006; 6:203-214.
15. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc* 1999; 74:877-884.
16. Waxman JE, Spector JG, Sale SR. Allergic aspergillus sinusitis: concepts in diagnosis and treatment of a new clinical entity. *Laryngoscope* 1987; 97:261-266.
17. Manning SC, Vuitch F, Weinberg AG, et al. Allergic aspergillosis: a newly recognized form of sinusitis in the pediatric population. *Laryngoscope* 1989; 99:681-685.
18. Goldstein MF. Allergic fungal sinusitis: an underdiagnosed problem. *Hosp Pract (Ed)* 1992; 27:73-92.
19. Ghegan MD, Lee F-S, Schlosser RJ. Incidence of skull base and orbital erosion in allergic fungal rhinosinusitis (AFRS) and non-AFRS. *Otolaryngol Head Neck Surg* 2006; 134:592-595.
20. Ferguson BJ. What role do systemic corticosteroids, immunotherapy, and antifungal drugs play in the therapy of allergic fungal rhinosinusitis? *Arch Otolaryngol Head Neck Surg* 1998; 124:1174-1177.
21. Mabry R, Marple BF, Folker RJ, et al. Immunotherapy for allergic fungal sinusitis: Three years' experience. *Otolaryngol Head Neck Surg* 1998; 119:648-651.

VII. MUCOCELES

1. Natvig K, Larsen TE. Mucocoele of the paranasal sinuses. A retrospective clinical and histological study. *J Laryngol Otol* 1978; 92:1075-1082.
2. East D. Mucocoeles of the maxillary antrum. Description, case reports and review of the literature. *J Laryngol Otol* 1985; 99:49-56.
3. Gardner DG, Gullane PJ. Mucocoeles of the maxillary sinuses. *Oral Surg Oral Med Oral Pathol* 1986; 62:538-543.
4. Stankiewicz JA. Sphenoid sinus mucocoele. *Arch Otolaryngol Head Neck Surg* 1989; 115:735-740.
5. Moriyama H, Nakajima T, Honda Y. Studies on mucocoeles of the ethmoid and sphenoid sinuses: analysis of 47 cases. *J Laryngol Otol* 1992; 106:23-27.
6. Marks SC, Latoni JD, Mathog RH. Mucocoeles of the maxillary sinus. *Otolaryngol Head Neck Surg* 1997; 117:18-21.
7. Bockmuhl U, Kratzsch B, Benda K, et al. Surgery for paranasal sinus mucocoeles: efficacy of endonasal microendoscopic management and long-term results of 185 patients. *Rhinology* 2006; 44:62-67.
8. Stiernberg CM, Bailey BJ, Calhoun KH, et al. Management of invasive frontoethmoidal sinus mucocoeles. *Arch Otolaryngol Head Neck Surg* 1986; 112:1060-1063.
9. Lund VJ, Milroy CM. Fronto-ethmoidal mucocoeles: a histopathological analysis. *J Laryngol Otol* 1991; 105:921-922.
10. Toriumi DM, Sykes JM, Russell EJ. Sphenothmoid mucocoele with intracranial extension: radiologic diagnosis. *Otolaryngol Head Neck Surg* 1988; 98:254-257.
11. Green DC, Calcaterra TC. Sphenothmoid sinus mucocoele presenting with amenorrhea and galactorrhea. *Otolaryngol Head Neck Surg* 1991; 104:856-857.
12. Crain MR, Dolan KD, Maves MD. Maxillary sinus mucocoele. *Ann Otol Rhinol Laryngol* 1990; 99:321-322.
13. Han MH, Chang KH, Lee CH, et al. Cystic expansile masses of the maxilla: differential diagnosis with CT and MR. *AJNR Am J Neuroradiol* 1995; 16:333-338.
14. Lidov M, Behin F, Som PM. Calcified sphenoid mucocoeles. *Arch Otolaryngol Head Neck Surg* 1990; 116:718-720.
15. Proto E, Cruz S, Puxeddu P. Histological and ultrastructural findings on mucocoele of maxillary sinus. *ORL* 1986; 48:345-350.
16. Josephson JS, Kennedy DW. Surgery of paranasal sinus mucocoeles. *Operative Techniques In Otolaryngology—Head Neck Surg* 1990; 1:133-141.

VIII. CHOLESTEROL GRANULOMA

1. Milton CM, Bickerton RC. A review of maxillary sinus cholesterol granuloma. *Brit J Oral Maxillofac Surg* 1986; 24:293-299.
2. Kunt T, Ozturkcan S, Egilmez R. Cholesterol granuloma of the maxillary sinus: six cases from the same region. *J Laryngol Otol* 1998; 112:65-68.
3. Leon ME, Chavez C, Fyfe B, et al. Cholesterol granuloma of the maxillary sinus. *Arch Pathol Lab Med* 2002; 126:217-219.
4. Bella Z, Torkos A, Tiszlavicz L, et al. Cholesterol granuloma of the maxillary sinus resembling an invasive, destructive tumor. *Eur Arch Otorhinolaryngol* 2005; 262:531-533.

5. Armengot M, Barona R, Garin L, et al. Ethmoid cholesterol granuloma. *Otolaryngol Head Neck Surg* 1993; 109:762–765.
6. Shykhon ME, Trotter MI, Morgan DW, et al. Cholesterol granuloma of the frontal sinus. *J Laryngol Otol* 2002; 116:1041–1043.
7. McNab AA, Wright JE. Orbitofrontal cholesterol granuloma. *Ophthalmology* 1990; 97:28–32.
8. Aferzon M, Millman B, O'Donnell TR, et al. Cholesterol granuloma of the frontal bone. *Otolaryngol Head Neck Surg* 2002; 127:578–581.

IX. MYOSPHERULOSIS

1. Kyriakos M, Conner DH, Neafie RC, et al. Myospherulosis. In: Binford CH, Conner DH, eds. *Pathology of Tropical and Extraordinary Diseases*. Vol 2. Washington, DC: Armed Forces Institute of Pathology, 1976:664–667.
2. Kyriakos M. Myospherulosis of the paranasal sinuses, nose and middle ear: a possible iatrogenic disease. *Am J Clin Pathol* 1977; 67:118–130.
3. Rosai J. The nature of myospherulosis of the upper respiratory tract. *Am J Clin Pathol* 1978; 69:475–481.
4. Wheeler TM, McGavran MH. Myospherulosis—further observations. *Am J Clin Pathol* 1978; 68:685–686.
5. Belfiglio EJ, Wonderlich ST, Fox LJ. Myospherulosis of the alveolus secondary to the use of Terra-cortril and Gelfoam. Report of a case. *Oral Surg Oral Med Oral Pathol* 1986; 61:12–14.
6. Paugh DR, Sullivan MJ. Myospherulosis of the paranasal sinuses. *Otolaryngol Head Neck Surg* 1990; 103:117–119.
7. Shimada K, Kobayashi S, Yamadori I, et al. Myospherulosis in Japan. A report of two cases and an immunohistochemical investigation. *Am J Surg Pathol* 1988; 12:427–432.
8. Kakizaki H, Shimada K. Experimental study of the cause of myospherulosis. *Am J Clin Pathol* 1993; 99:249–256.
9. Schryver-Kecskemeti KD, Kyriakos M. Myospherulosis: an electron microscopic study of a human case. *Am J Clin Pathol* 1977; 67:555–561.
10. McClatchie S, Warambo MW, Bremner AD. Myospherulosis: a previously unreported disease? *Am J Clin Pathol* 1969; 51:699–704.
11. Ferrell LD. Myospherulosis of the breast: diagnosis by fine needle aspiration. *Acta Cytol* 1984; 28:726–728.
12. Young PN. Spontaneous myospherulosis developing at contact with a mature cystic dysembryoma of the ovary: pathogenetic discussion apropos of a case diagnosed by laparoscopic biopsy. *J Gynecol Obstet Biol Reprod (Paris)* 1988; 17:15–18.
13. Chait DH, Katz DA. Myospherulosis. *Nebr Med* 1985; 70:57–60.
14. Travis WD, Li C-Y, Weiland LH. Immunostaining for hemoglobin in two cases of myospherulosis. *Arch Pathol Lab Med* 1986; 110:763–765.
15. Panayiotopoulou M, Freedman PD, Weber F, et al. The synchronous occurrence of aspergillosis and myospherulosis of the maxillary sinus. Report of a case with review of the literature. *Oral Surg Oral Med Oral Pathol* 1987; 63:582–585.
- granuloma faciale? A report of three cases. *Histopathology* 1985; 9:1217–1225.
3. Fageeh NA, Mai KT, Odell PF. Eosinophilic angiocentric fibrosis of the subglottic region of the larynx and the upper trachea. *J Otolaryngol* 1996; 25:276–278.
4. Altemani AM, Pilch BZ, Sakano E, et al. Eosinophilic angiocentric fibrosis of the nasal cavity. *Mod Pathol* 1997; 10:391–393.
5. Matai V, Baer S, Barnes S, et al. Eosinophilic angiocentric fibrosis. *J Laryngol Otol* 2000; 114:563–564.
6. Thompson LDR, Heffner DK. Sinonasal tract eosinophilic angiocentric fibrosis. A report of three cases. *Am J Clin Pathol* 2001; 115:243–248.
7. Loane J, Jaramillo M, Young HA, et al. Eosinophilic angiocentric fibrosis and Wegener's granulomatosis: a case report and literature review. *J Clin Pathol* 2001; 54:640–641.
8. Burns BV, Robert PF, DeCarpentier J, et al. Eosinophilic angiocentric fibrosis affecting the nasal cavity. A mucosal variant of the skin lesion granuloma faciale. *J Laryngol Otol* 2001; 115:223–221.
9. Pereira EM, Millas I, Reis-Filho JS, et al. Eosinophilic angiocentric fibrosis of the sinonasal tract: report on the clinicopathologic features of a case and review of the literature. *Head Neck* 2002; 24:307–311.
10. Goldman NC. Angiocentric eosinophilic fibrosis. *Otolaryngol Head Neck Surg* 2003; 128:445–446.
11. Tabae A, Zadeh MH, Proytcheva M, et al. Eosinophilic angiocentric fibrosis. *J Laryngol Otol* 2003; 117:410–413.
12. Nguyen DB, Alex JC, Calhoun B. Eosinophilic angiocentric fibrosis in a patient with nasal obstruction. *ENT J* 2004; 83:183–186.
13. Narayan J, Douglas-Jones AG. Eosinophilic angiocentric fibrosis and granulomas faciale: analysis of cellular infiltrate and review of the literature. *Ann Otol Rhinol Laryngol* 2005; 114:35–42.
14. Paun S, Lund VJ, Gallimore A. Nasal fibrosis: long term follow up of four cases of eosinophilic angiocentric fibrosis. *J Laryngol Otol* 2005; 119:119–124.
15. Leibovitch I, James CL, Wormald PJ, et al. Orbital eosinophilic angiocentric fibrosis. Case report and review of the literature. *Ophthalmology* 2006; 113:148–152.

XI. RESPIRATORY EPITHELIAL ADENOMATOID HAMARTOMA

1. Baillie EE, Batsakis JG. Glandular (seromucinous) hamartoma of the nasopharynx. *Oral Surg Oral Med Oral Pathol* 1974; 38:760–762.
2. Graeme-Cook F, Pilch BZ. Hamartomas of the nose and nasopharynx. *Head Neck* 1992; 14:321–327.
3. Terris MH, Billman GF, Pransky SM. Nasal hamartoma: case report and review of the literature. *Int J Pediatr Otorhinolaryngol* 1993; 28:83–88.
4. Wenig BM, Heffner DK. Respiratory epithelial adenomatoid hamartomas of the sinonasal tract and nasopharynx: a clinicopathologic study of 31 cases. *Ann Otol Rhinol Laryngol* 1995; 104:639–645.
5. Adair CF, Thompson LDR, Wenig BM, et al. Chondroosseous and respiratory epithelial hamartomas of the sinonasal tract and nasopharynx [abstr]. *Lab Invest* 1996; 74:100A.

X. EOSINOPHILIC ANGIOCENTRIC FIBROSIS

1. Holmes DK, Panje WR. Intranasal granuloma faciale. *Am J Otolaryngol* 1983; 4:184–186.
2. Roberts PF, McCann BG. Eosinophilic angiocentric fibrosis of the upper respiratory tract: a mucosal variant of

XII. SCHNEIDERIAN PAPILLOMAS

1. Ward N. A mirror of the practice of medicine and surgery in the hospitals of London: London Hospital. *Lancet* 1854; 2:480–482.

2. Hyams VJ. Papillomas of the nasal cavity and paranasal sinuses. A clinicopathologic study of 315 cases. *Ann Otol Rhinol Laryngol* 1971; 80:192-206.
3. Snyder RN, Perzin KH. Papillomatosis of nasal cavity and paranasal sinuses (inverted papilloma, squamous papilloma). A clinicopathologic study. *Cancer* 1971; 30:668-690.
4. Weissler MC, Montgomery WW, Turner PA, et al. Inverted papilloma. *Ann Otol Rhinol Laryngol* 1986; 95:215-221.
5. Michaels L, Young M. Histogenesis of papillomas of the nose and paranasal sinuses. *Arch Pathol Lab Med* 1995; 119:821-826.
6. Michaels L. Benign mucosal tumors of the nose and paranasal sinuses. *Semin Diagn Pathol* 1996; 13:113-117.
7. Lampertico P, Russell WO, MacComb WS. Squamous papilloma of the upper respiratory epithelium. *Arch Pathol* 1963; 75:293-302.
8. Oberman HA. Papillomas of the nose and paranasal sinuses. *Am J Clin Pathol* 1964; 42:245-258.
9. Vrabec DP. The inverted Schneiderian papilloma. A 25-year study. *Laryngoscope* 1994; 104:582-605.
10. Fu YS, Hoover L, Franklin M, et al. Human papillomavirus identified by nucleic acid hybridization in concomitant nasal and genital papillomas. *Laryngoscope* 1992; 102:1014-1019.
11. Buchwald C, Franzman M-B, Jacobsen GK, et al. Human papillomavirus (HPV) in sinonasal papillomas: a study of 78 cases using in situ hybridization and polymerase chain reaction. *Laryngoscope* 1995; 105:66-71.
12. Weiner JS, Sherris D, Kasperbauer J, et al. Relationship of human papillomavirus to Schneiderian papilloma. *Laryngoscope* 1999; 109:21-26.
13. Norris HJ. Papillary lesions of the nasal cavity and paranasal sinuses. Part I. Exophytic (squamous) papillomas. A study of 28 cases. *Laryngoscope* 1962; 72:1784-1797.
14. Christensen WN, Smith RRL. Schneiderian papillomas: a clinicopathologic study of 67 cases. *Hum Pathol* 1986; 17:393-400.
15. Buchwald C, Franzman M-B, Tos M. Sinonasal papillomas: a report of 82 cases in Copenhagen County, including a longitudinal, epidemiological and clinical study. *Laryngoscope* 1995; 105:72-79.
16. Hirschfield LS, Harrison G. Human papillomavirus in sinonasal papillomas [abstr]. *Mod Pathol* 1990; 3:45A.
17. Judd R, Zaki SR, Coffield LM, et al. Sinonasal papillomas and human papillomavirus: human papillomavirus 11 detected in fungiform Schneiderian papillomas by in situ hybridization and the polymerase chain reaction. *Hum Pathol* 1991; 22:550-556.
18. Kashima HK, Kessis T, Hruban RH, et al. Human papillomavirus in sinonasal papillomas and squamous cell carcinoma. *Laryngoscope* 1992; 102:973-976.
19. McLachlin CM, Kandel RA, Colgan TJ, et al. Prevalence of human papillomavirus in sinonasal papillomas: a study using polymerase chain reaction and in situ hybridization. *Mod Pathol* 1992; 5:406-409.
20. Sarkar FH, Visscher DW, Kintanar EB, et al. Sinonasal Schneiderian papillomas: human papillomavirus typing by polymerase chain reaction. *Mod Pathol* 1992; 5:329-332.
21. Wu T-C, Trujillo JM, Kasima HK. Association of human papillomavirus with nasal neoplasia. *Lancet* 1993; 341:522-524.
22. Gaffey MJ, Frierson HF Jr, Weiss LM, et al. Prevalence of Epstein-Barr virus (EBV) and human papillomavirus (HPV) in sinonasal papillomas: an in-situ hybridization (ISH) study [abstr]. *Lab Invest* 1996; 74:101A.
23. Buchwald C, Franzmann M-B, Jacobson GK, et al. Carcinomas occurring in papillomas of the nasal septum with human papillomavirus (HPV). *Rhinology* 1997; 35:74-78.
24. Suh KW, Facer GW, Devine KD, et al. Inverting papilloma of the nose and paranasal sinuses. *Laryngoscope* 1977; 87:35-46.
25. Lawson W, Le Bengier J, Som P, et al. Inverted papilloma: an analysis of 87 cases. *Laryngoscope* 1989; 99:1117-1124.
26. Myers EN, Fernau JL, Johnson JT, et al. Management of inverted papilloma. *Laryngoscope* 1990; 100:481-490.
27. Phillips PP, Gustafson RO, Facer GW. The clinical behavior of inverted papilloma of the nose and paranasal sinuses: report of 112 cases and review of the literature. *Laryngoscope* 1990; 100:463-469.
28. Outsen KE, Grontved A, Jorgensen K, et al. Inverted papilloma of the nose and paranasal sinuses: a study of 67 patients. *Clin Otolaryngol* 1991; 16:309-312.
29. Dolgin SR, Zaveri VD, Casiano RR, et al. Different options for treatment of inverting papilloma of the nose and paranasal sinuses: a report of 41 cases. *Laryngoscope* 1992; 102:231-236.
30. Bielamowicz S, Calcaterra TC, Watson D. Inverting papilloma of the head and neck: the UCLA update. *Otolaryngol Head Neck Surg* 1993; 109:71-76.
31. Lawson W, Ho BT, Shaari CM, et al. Inverted papilloma: a report of 112 cases. *Laryngoscope* 1995; 105:282-288.
32. Eavey RD. Inverted papilloma of the nose and paranasal sinuses in childhood and adolescence. *Laryngoscope* 1985; 95:17-22.
33. Peters BW, O'Reilly RC, Willcox TO Jr, et al. Inverted papilloma isolated to the sphenoid sinus. *Otolaryngol Head Neck Surg* 1995; 113:771-781.
34. Kelley JH, Joseph M, Carroll E, et al. Inverted Papilloma of the nasal septum. *Arch Otolaryngol* 1980; 106:767-771.
35. Sulica RL, Wenig BM, Debo RF, et al. Schneiderian papillomas of the pharynx. *Ann Otol Rhinol Laryngol* 1999; 108:392-397.
36. Radcliffe A. Transitional cell papilloma of the postpharyngeal wall. *J Laryngol Otol* 1953; 67:682-688.
37. Hampal S, Hawthorne M. Hypopharyngeal inverted papilloma. *J Laryngol Otol* 1990; 104:432-434.
38. Astor FC, Donegan O, Gluckman JL. Unusual anatomic presentations of inverting papilloma. *Head Neck Surg* 1985; 7:243-245.
39. Ryan SJ, Font RL. Primary epithelial neoplasms of the lacrimal sac. *Am J Ophthalmol* 1973; 76:73-88.
40. Wenig BM. Schneiderian-type mucosal papillomas of the middle ear and mastoid. *Ann Otol Rhinol Laryngol* 1996; 105:226-233.
41. Fechner RE, Sessions RE. Inverted papilloma of the lacrimal sac, the paranasal sinuses and the cervical region. *Cancer* 1977; 40:2303-2308.
42. Respler DS, Jahn A, Pater A, et al. Isolation and characterization of papillomavirus DNA from nasal inverting (Schneiderian) papillomas. *Ann Otol Rhinol Laryngol* 1987; 96:170-173.
43. Syrjanen S, Happonen R-P, Virolainen E, et al. Detection of human papillomavirus (HPV) structural antigens and DNA types in inverted papillomas and squamous cell carcinomas of the nasal cavities and paranasal sinuses. *Acta Otolaryngol* 1987; 104:334-341.
44. Weber RS, Shillitoe EJ, Robbins KT, et al. Prevalence of human papillomavirus in inverted nasal papillomas. *Arch Otolaryngol Head Neck Surg* 1988; 114:23-26.
45. Brandwein M, Steinberg B, Thung S, et al. Human Papillomavirus 6/11 and 16/18 in Schneiderian inverted papillomas. In situ hybridization with human papillomavirus RNA probes. *Cancer* 1989; 63:1708-1713.
46. Bryan RL, Bovan IS, Crocker J, et al. Detection of HPV 6 and 11 in tumours of the upper respiratory tract using

- the polymerase chain reaction. *Clin Otolaryngol* 1990; 15:177-180.
47. Kleini PJ, Joensuu H, Siivonen L, et al. Association of DNA aneuploidy with human papillomavirus-induced malignant transformation of sinonasal transitional papillomas. *Otolaryngol Head Neck Surg* 1989; 100:563-567.
 48. Siivonen L, Virolainen E. Transitional papilloma of the nasal cavity and paranasal sinuses. Clinical course, viral etiology and malignant transformation. *ORL J Otorhinolaryngol Relat Spec* 1989; 51:262-267.
 49. Ishibashi T, Tsunokawa Y, Matsushima S, et al. Presence of human papillomavirus type 6-related sequences in inverted nasal papillomas. *Eur Arch Otorhinolaryngol* 1990; 247:296-299.
 50. Furuta Y, Shinohara T, Sano K, et al. Molecular pathologic study of human papillomavirus infection in inverted papilloma and squamous cell carcinoma of the nasal cavities and paranasal sinuses. *Laryngoscope* 1991; 101:79-85.
 51. Beck JC, McClatchey KD, Lesperance MM, et al. Presence of human papillomavirus predicts recurrence of inverted papilloma. *Otolaryngol Head Neck Surg* 1995; 113:49-55.
 52. Ogura H, Fujiwara T, Hamaya K, et al. Detection of human papillomavirus type 57 in a case of inverted nasal papillomatosis in Japan. *Eur Arch Otorhinolaryngol* 1995; 252:513-515.
 53. Macdonald MR, Le KT, Freeman J, et al. A majority of inverted sinonasal papillomas carries Epstein-Barr virus genomes. *Cancer* 1995; 75:2307-2312.
 54. Momose KJ, Weber AI, Goodman M, et al. Radiologic aspects of inverted papilloma. *Radiology* 1980; 134:73-79.
 55. Norris HJ. Papillary lesions of the nasal cavity and paranasal sinuses. Part II. Inverting papillomas. A study of 29 cases. *Laryngoscope* 1963; 73:1-17.
 56. Abildgaard-Jensen J, Greisen O. Inverted papillomas of the nose and the paranasal sinuses. *Clin Otolaryngol* 1985; 10:135-143.
 57. Myers EN, Schramm VL Jr, Barnes EL Jr. Management of inverted papillomas of the nose and paranasal sinuses. *Laryngoscope* 1981; 91:2071-2084.
 58. Orvidas LJ, Lewis JE, Olsen KD, et al. Intranasal verrucous carcinoma: relationship to inverting papillomas and the human papillomavirus. *Laryngoscope* 1999; 109:371-375.
 59. Skolnik EM, Loewy A, Friedman JE. Inverted papilloma of the nasal cavity. *Arch Otolaryngol* 1966; 84:83-89.
 60. Lasser A, Rothfeld PR, Shapiro RS. Epithelial papilloma and squamous cell carcinoma of the nasal cavity and paranasal sinuses. A clinicopathologic study. *Cancer* 1976; 38:2503-2510.
 61. Woodson GE, Robbins KT, Michaels L. Inverted papilloma. Considerations in treatment. *Arch Otolaryngol* 1985; 111:806-811.
 62. Segal K, Atar E, Mor C, et al. Inverting papilloma of the nose and paranasal sinuses. *Laryngoscope* 1986; 96:394-398.
 63. Lesperance MM, Esclamado RM. Squamous cell carcinoma arising in inverted papilloma. *Laryngoscope* 1995; 105:178-183.
 64. Schwerer MJ, Sailer A, Kraft, et al. Differentiation-related p53 protein expression in nondysplastic sinonasal inverted papillomas. *Am J Rhinol* 2001; 15:347-351.
 65. Mirza N, Montone K, Sato Y, et al. Identification of p53 and human papillomavirus in Schneiderian papillomas. *Laryngoscope* 1998; 108:497-501.
 66. Ingle R, Jennings TA, Goodman ML, et al. CD44 expression in sinonasal inverted papillomas and associated squamous cell carcinoma. *Am J Clin Pathol* 1998; 109:309-314.
 67. Califano J, Koch W, Sidransky D, et al. Inverted sinonasal papilloma. A molecular genetic appraisal of its putative status as a precursor to squamous cell carcinoma. *Am J Pathol* 2000; 156:333-337.
 68. Van Olphen AF, Lubsen H, van't Verlaat JW. An inverted papilloma with intracranial extension. *J Laryngol Otol* 1988; 102:534-537.
 69. Busquets JM, Hwang PH. Endoscopic resection of sinonasal inverted papilloma: a meta-analysis. *Otolaryngol Head Neck Surg* 2006; 134:476-483.
 70. Krouse JH. Development of a staging system for inverted papilloma. *Laryngoscope* 2000; 110:965-968.
 71. Mendenhall WM, Million RR, Cassisi NJ, et al. Biologically aggressive papillomas of the nasal cavity: the role of radiation therapy. *Laryngoscope* 1985; 95:344-347.
 72. Ridolfi RL, Lieberman PH, Erlandson RA, et al. Schneiderian papillomas: a clinicopathologic study of 30 cases. *Am J Surg Pathol* 1977; 1:43-53.
 73. Barnes L, Bedetti C. Oncocytic Schneiderian papilloma: a reappraisal of cylindrical cell papilloma of the sinonasal tract. *Hum Pathol* 1984; 15:344-351.
 74. DeBoom GW, Jensen JL, Wuerker RB. Cylindrical cell papilloma. *Oral Surg Oral Med Oral Pathol* 1986; 61:607-610.
 75. Kusakari J, Hozawa K, Hanazima T, et al. Clinical report: cylindrical cell papilloma of the paranasal sinus. *Arch Otorhinolaryngol* 1987; 244:246-248.
 76. Cunningham MJ, Brantley S, Barnes L, et al. Oncocytic Schneiderian papilloma in a young adult: a rare diagnosis. *Otolaryngol Head Neck Surg* 1987; 97:47-51.
 77. Ward BE, Fechner RE, Mills SE. Carcinoma arising in oncocytic Schneiderian carcinoma. *Am J Surg Pathol* 1990; 14:364-369.
 78. Kapadia SB, Barnes L, Pelzman K, et al. Carcinoma ex oncocytic Schneiderian (cylindrical cell) papilloma. *Am J Otolaryngol* 1993; 14:332-338.
 79. Maitra A, Baskin LB, Lee EL. Malignancies arising in oncocytic Schneiderian papillomas. A report of 2 cases and review of the literature. *Arch Pathol Lab Med* 2001; 125:1365-1367.

XIII. SQUAMOUS CELL CARCINOMA OF THE NASAL CAVITY

1. Tufano RP, Mokadam NA, Montone KT, et al. Malignant tumors of the nose and paranasal sinuses: Hospital of the University of Pennsylvania experience 1990-1997. *Am J Rhinol* 1999; 13:117-123.
2. Calderon-Garciduenas L, Delgado R, Calderon-Garciduenas A, et al. Malignant neoplasms of the nasal cavity and paranasal sinuses: a series of 256 patients in Mexico city and Monterrey. Is air pollution the missing link? *Otolaryngol Head Neck Surg* 2000; 122:499-508.
3. Dulguerov P, Jacobsen MS, Allal AS, et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001; 92:3012-3029.
4. Bhattachryya N. Cancer of the nasal cavity. Survival and factors influencing survival. *Arch Otolaryngol Head Neck Surg* 2002; 128:1079-1083.
5. Carrillo JF, Guemes A, Ramirez-Ortega MC, et al. Prognostic factors in maxillary and nasal carcinoma. *Eur J Surg Oncol* 2005; 31: 1206-1212.
6. Buchanan G, Slavin G. Tumors of the nose and sinuses. A clinicopathologic study. *J Laryngol Otol* 1972; 86:685-696.
7. Batsakis JG, Rice DH, Solomon AR. The pathology of head and neck tumors: squamous and mucous-gland

- carcinomas of the nasal cavity, paranasal sinuses and larynx, Part 6. *Head Neck Surg* 1980; 2:497-508.
8. Sisson GA, Becker SP. Cancer of the nasal cavity and the paranasal sinuses. In: Suen JY, Myers EN, eds. *Cancer of the Head and Neck*. New York: Churchill Livingstone, 1981: 242-279.
9. Lewis JS, Castro EB. Cancer of the nasal cavity and paranasal sinuses. *J Laryngol Otol* 1972; 86:255-262.
10. Robin PE, Powell DJ. Regional node involvement and distant metastases in carcinoma of the nasal cavity and paranasal sinuses. *J Laryngol Otol* 1980; 94:301-309.
11. Rousch GC. Epidemiology of cancer of the nose and paranasal sinuses: current concepts. *Head Neck Surg* 1979; 2:3-11.
12. Lareo AC, Luce D, Luclerc A, et al. History of previous nasal diseases and sinonasal cancer: a case-control study. *Laryngoscope* 1992; 102:439-442.
13. Furuta Y, Takasu T, Asai T, et al. Detection of human papillomavirus DNA in carcinomas of the nasal cavities and paranasal sinuses by polymerase chain reaction. *Cancer* 1992; 69:353-357.
14. Paulino AF, Singh B, Carew J, et al. Epstein-Barr virus in squamous carcinoma of the anterior nasal cavity. *Ann Diagn Pathol* 2000; 4:7-10.
15. MacComb WS, Martin HE. Cancer of the nasal cavity. *Am J Roentgenol Radium Ther Nucl Med* 1942; 47:11-23.
16. Parker RG. Carcinoma of the nasal fossa. *Am J Roentgenol Radium Ther Nucl Med* 1958; 80:766-774.
17. Deutsch HJ. Carcinoma of the nasal septum. Report of a case and review of the literature. *Ann Otol Rhinol Laryngol* 1966; 75:1049-1057.
18. DesPrez JD, Kiehn CI. Carcinoma of the nasal vestibule. *Am J Surg* 1967; 114:587-591.
19. Boone MLM, Harle TS, Higholt HW, et al. Malignant disease of the paranasal sinuses and nasal cavity. Importance of precise localization and extent of disease. *Am J Roentgenol Radium Ther Nucl Med* 1968; 102:627-636.
20. Whitcomb WP. Radiation therapy of carcinoma of the anterior nasal cavity. *Am J Roentgenol Radium Ther Nucl Med* 1969; 105:550-554.
21. Badib AO, Kurohara SS, Webster JH, et al. Treatment of cancer of the nasal cavity. *Am J Roentgenol Radium Ther Nucl Med* 1969; 106:824-830.
22. Goepfert H, Guillemandegui OM, Jesse RH, et al. Squamous cell carcinoma of nasal vestibule. *Arch Otolaryngol* 1974; 100:8-10.
23. Haynes WD, Tapley N. Radiation treatment of carcinoma of the nasal vestibule. *Am J Roentgenol Radium Ther Nucl Med* 1974; 120:595-602.
24. Wang CC. Treatment of carcinoma of the nasal vestibule by irradiation. *Cancer* 1976; 37:1458-1463.
25. Bosch A, Vallecillo L, Frias Z. Cancer of the nasal cavity. *Cancer* 1976; 37:1458-1463.
26. Weimert TA, Batsakis JG, Rice DH. Carcinomas of the nasal septum. *J Laryngol Otol* 1978; 92:209-213.
27. Mak ACA, van Andel JG, van Woerkom-Eijkenboom WMH, et al. Radiation therapy of carcinoma of the nasal vestibule. *Eur J Cancer* 1979; 16:81-85.
28. Ellingwood KE, Million RR. Cancer of the nasal cavity and ethmoid/sphenoid sinuses. *Cancer* 1979; 43L: 1517-1526.
29. Schaefer SD, Hill GC. Epidermoid carcinoma of the nasal vestibule: current treatment evaluation. *Laryngoscope* 1980; 90:1631-1635.
30. Chung CT, Rabuzzi DD, Sagerman RH, et al. Radiotherapy for carcinoma of the nasal cavity. *Arch Otolaryngol* 1980; 106:763-766.
31. Kagan AR, Nussbaum H, Rao A, et al. The management of carcinoma of the nasal vestibule. *Head Neck Surg* 1981; 4:125-128.
32. Beatty CW, Pearson BW, Kern EB. Carcinoma of the nasal septum: experience with 85 cases. *Otolaryngol Head Neck Surg* 1982; 90:90-94.
33. LeLievre WC, Bailey BJ, Griffiths C. Carcinoma of the nasal septum. *Arch Otolaryngol* 1984; 110:748-751.
34. Johansen LV, Hjelm-Hansen M, Anderson AP. Squamous cell carcinoma of the nasal vestibule. Treatment results. *Acta Radiol Oncol* 1984; 23:189-192.
35. Schalekamp W, Hordijk GJ. Carcinoma of the nasal vestibule: prognostic factors in relation to lymph node metastasis. *Clin Otolaryngol* 1985; 10:210-203.
36. Wong CS, Cummings BJ, Elhakim T, et al. External irradiation for squamous cell carcinoma of the nasal vestibule. *Int J Radiat Oncol Biol Phys* 1986; 12:1943-1946.
37. Shidnia H, Hartsough AB, Weisberger E, et al. Epithelial carcinoma of the nasal fossa. *Laryngoscope* 1987; 97: 717-723.
38. Mendenhall NP, Parsons JT, Cassisi NJ, et al. Carcinoma of the nasal vestibule treated with radiation therapy. *Laryngoscope* 1987; 97:626-632.
39. Hawkins RB, Wynstra JH, Pilepich MV, et al. Carcinoma of the nasal cavity—results of primary and adjunct radiotherapy. *Int J Radiat Oncol Biol Phys* 1988; 15:1129-1133.
40. Parsons JT, Mendenhall WM, Mancuso AA, et al. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. *Int J Radiat Oncol Biol Phys* 1988; 14:11-22.
41. Chobe R, McNeese M, Weber R, et al. Radiation therapy for carcinoma of the nasal vestibule. *Otolaryngol Head Neck Surg* 1988; 98:67-71.
42. Spiro JD, Soo KC, Spiro RH. Squamous carcinoma of the nasal cavity and paranasal sinuses. *Am J Surg* 1989; 158:328-332.
43. Patel P, Tiwari R, Karim ABMF, et al. Squamous cell carcinoma of the nasal vestibule. *J Laryngol Otol* 1992; 106:332-336.
44. Barzan L, Franchin G, Frustaci S, et al. Carcinoma of the nasal vestibule. Report of 12 cases. *J Laryngol Otol* 1990; 104:9-11.
45. Poulsen M, Turner S. Radiation therapy for squamous cell carcinoma of the nasal vestibule. *Int J Radiat Oncol Biol Phys* 1993; 27:267-272.
46. McCollough WM, Mendenhall NP, Parsons JT, et al. Radiotherapy alone for squamous cell carcinoma of the nasal vestibule: management of the primary site and regional lymphatics. *Int J Radiat Oncol Biol Phys* 1993; 26:73-79.
47. Fradis M, Podoshin L, Gertner R, et al. Squamous cell carcinoma of the nasal septum mucosa. *Ear Nose Throat J* 1993; 72:217-221.
48. Sakashita M, Nakajima T, Tsumura M, et al. Radiotherapy for squamous cell carcinoma of the nasal cavity. *Radiat Oncol* 1993; 11:91-94.
49. Pantelakos ST, McGuirt WF, Nussear DW. Squamous cell carcinoma of the nasal vestibule and anterior nasal passages. *Am J Otolaryngol* 1994; 15:33-36.
50. Mendenhall WM, Stringer SP, Cassisi NJ, et al. Squamous cell carcinoma of the nasal vestibule. *Head Neck* 1999; 21:385-393.
51. Horsmans JDJ, Godballe C, Jorgensen KE, et al. Squamous cell carcinoma of the nasal vestibule. *Rhinology* 1999; 37:117-121.
52. Samaha M, Yoskovitch A, Hier MP, et al. Squamous cell carcinoma of the nasal vestibule. *J Otolaryngol* 2000; 29: 98-101.

53. Kummer E, Rasch CRN, Keus RB, et al. T Stage as prognostic factor in irradiated localized squamous cell carcinoma of the nasal vestibule. *Head Neck* 2002; 24: 268–273.
54. Landgrendijk JA, Poorter R, Leemans CR, et al. Radiotherapy of squamous cell carcinoma of the nasal vestibule. *Int J Radiat Oncol Biol Phys* 2004; 59: 1319–1325.
55. DiLeo MD, Miller RH, Rice JC, et al. Nasal septal squamous cell carcinoma: a chart review and meta-analysis. *Laryngoscope* 1996; 106:1218–1222.
56. Fornelli RA, Fedok FG, Wilson EP, et al. Squamous cell carcinoma of the anterior nasal cavity: a dual institution review. *Otolaryngol Head Neck Surg* 2000; 123:207–210.
57. Lederman M. Cancer of the upper jaw and nasal chambers. *Proc R Soc Med* 1969; 62:65–72.
58. Robin RE. Lateralization of the tumours of the nasal cavity and paranasal sinuses and its relationship to etiology. *Lancet* 1979; 1:695–696.
59. American Joint Commission Cancer Staging Manual, 6th edition, Greene FL, Page DL, Fleming ID, et al. eds, New York: Springer 2002:203–208.
14. Stern SJ, Goepfert H, Clayman G, et al. Squamous cell carcinoma of the maxillary sinus. *Arch Otolaryngol Head Neck Surg* 1993; 119:964–969.
15. Shibuya H, Hoshima M, Shagdarsuren M, et al. Squamous cell carcinoma of the maxillary sinus and the oral part of the upper jaw. Comparison of treatment results. *Acta Oncol* 1994; 33:43–47.
16. Miyaguchi M, Sakai S-I, Takashima H, et al. Lymph node and distant metastases in patients with sinonasal carcinomas. *J Laryngol Otol* 1995; 109:304–407.
17. Alvarez I, Suarez C, Rodrigo JP, et al. Prognostic factors in paranasal sinus cancer. *Am J Otolaryngol* 1995; 16:109–114.
18. Paulino AC, Marks JE, Bricker P, et al. Results of treatment of patients with maxillary sinus carcinoma. *Cancer* 1998; 83:457–465.
19. Le Q-T, Fu KK, Kaplan M, et al. Treatment of maxillary sinus carcinoma. A comparison of the 1997 and 1977 American Joint Committee on Cancer Staging Systems. *Cancer* 1999; 86:1700–1711.
20. Hayashi T, Nonaka S, Bandoh N, et al. Treatment outcome of maxillary sinus squamous cell carcinoma. *Cancer* 2001; 92:1495–1503.
21. Nibu K-I, Suqasawa M, Asai M, et al. Results of multimodality therapy for squamous cell carcinoma of maxillary sinus. *Cancer* 2002; 94:1476–1483.
22. Kondo M, Inuyama Y, Ando Y, et al. Patterns of relapse of squamous cell carcinoma of the maxillary sinus. *Cancer* 1984; 53:2206–2210.
23. Spiro JD, Soo KC, Spiro RH. Squamous carcinoma of the nasal cavity and paranasal sinuses. *Am J Surg* 1989; 158:328–332.
24. Zamora RL, Harvey JE, Sessions DG, et al. Clinical classification and staging for primary malignancies of the maxillary antrum. *Laryngoscope* 1990; 100:1106–1111.
25. Robin PE, Powell DJ. Regional node involvement and distant metastases in carcinoma of the nasal cavity and paranasal sinuses. *J Laryngol Otol* 1980; 94:301–309.
26. Chaudhry AP, Gorlin RJ, Mosser DG. Carcinoma of the antrum. A clinical and histopathologic study. *Oral Surg Oral Med Oral Pathol* 1960; 13:269–281.
27. Larsson LG, Martensson G. Carcinoma of the paranasal sinuses and the nasal cavities. A Clinical study of 379 cases treated at Radiumhemmet and the Otolaryngologic Department of Karolinska Sjukhuset, 1940–1950. *Acta Radiol* 1954; 42:149–172.
28. Shibuya H, Amagasa T, Hanai A, et al. Second primary carcinomas in patients with squamous cell carcinoma of the maxillary sinus. *Cancer* 1986; 58:1122–1125.
29. Miyaguchi M, Sakai S-I, Mori N, et al. Multiple primary malignancies in patients with malignant tumors of the nasal cavities and paranasal sinuses. *J Laryngol Otol* 1990; 104:696–698.
30. Sakaguchi M, Moriaya K, Taguchi K, et al. Bilateral carcinomas of the maxillary sinus. *J Laryngol Otol* 1993; 107:42–43.
31. Kondo M, Ando Y, Inuyama Y, et al. Maxillary squamous cell carcinoma staged by computed tomography. *Int J Radiat Oncol Biol Phys* 1986; 12:111–116.
32. Schellhas KP, EL Deeb M, Wilkes CH, et al. Three-dimensional computed tomography in maxillofacial surgical planning. *Arch Otolaryngol Head Neck Surg* 1988; 114:438–442.
33. Toriumi DM, Friedman CD, Sisson GA Sr. Carcinoma of the maxillary sinus with pterygoid invasion. *Ann Otol Rhinol Laryngol* 1989; 98:485–486.
34. Matsumoto S, Shibuya H, Tatera S, et al. Comparison of CT findings in non-Hodgkin's lymphoma and squamous

XIV. SQUAMOUS CELL CARCINOMA OF MAXILLARY SINUS

1. Pearson BW. The surgical anatomy of maxillectomy. *Surg Clin N Am* 1977; 57:701–721.
2. American Joint Committee on Cancer. Cancer Staging Manual, 6th ed, Greene FL, Page DL, Fleming ID, et al, eds. New York: Springer, 2002:59–67.
3. Pezner RD, Moss WT, Tong D, et al. Cervical lymph node metastases in patients with squamous cell carcinoma of the maxillary antrum: the role of elective irradiation of the clinically negative neck. *Int J Radiat Oncol Biol Phys* 1979; 5:1977–1980.
4. Sakai S, Hohki A, Fuchihata H, et al. Multidisciplinary treatment of maxillary sinus carcinoma. *Cancer* 1983; 52:1360–1364.
5. St-Pierre S, Baker SR. Squamous cell carcinoma of the maxillary sinus: analysis of 66 cases. *Head Neck Surg* 1983; 5:508–513.
6. Shibuya H, Horiuchi J-I, Suzuki S, et al. Maxillary sinus carcinoma: result of radiation therapy. *Int J Radiat Oncol Biol Phys* 1984; 10:1021–1026.
7. Hordijk GJ, Brons EN. Carcinomas of the maxillary sinus: a retrospective study. *Clin Oncol* 1985; 10:285–288.
8. Knegt PP, DeJong PC, van Andel JG, et al. Carcinoma of the paranasal sinuses. Results of a prospective pilot study. *Cancer* 1985; 56:57–62.
9. Lindeman P, Eklund U, Petruson B. Survival after surgical treatment in maxillary neoplasms of epithelial origin. *J Laryngol Otol* 1987; 101:564–568.
10. Lavertu P, Roberts JK, Kraus DH, et al. Squamous cell carcinoma of the paranasal sinuses: the Cleveland Clinic experience 1977–1986. *Laryngoscope* 1989; 99:1130–1136.
11. Sisson GA Sr, Toriumi DM, Atiyah RA. Paranasal sinus malignancy: a comprehensive update. *Laryngoscope* 1989; 99:143–150.
12. Miyaguchi M, Sakai S, Mori N, et al. Symptoms in patients with maxillary sinus carcinoma. *J Laryngol Otol* 1990; 104:557–559.
13. Giri SPG, Reddy EK, Gemer LS, et al. Management of advanced squamous cell carcinomas of the maxillary sinus. *Cancer* 1992; 69:657–661.

- cell carcinoma of the maxillary sinus. *Acta Radiol* 1992; 33:523-527.
35. Robin PE, Powell DJ. Diagnostic errors in cancers of the nasal cavity and paranasal sinuses. The essential role of surgery. *Arch Otolaryngol* 1941; 107:138-140.
 36. LoRusso P, Tapazoglou E, Kish JA, et al. Chemotherapy for paranasal sinus carcinoma. A 10-year experience at Wayne State University. *Cancer* 1988; 62:1-5.
 37. Janecka IP, Sen C, Sekhar L, et al. Treatment of paranasal sinus cancer with cranial base surgery: results. *Laryngoscope* 1994; 104:553-555.
 38. Sakai S-I, Kubo T, Mori N, et al. A study of late effects of radiotherapy and operation on patients with maxillary cancer. A survey more than 10 years after initial treatment. *Cancer* 1988; 62:2114-2117.
 39. Sakata K-I, Aoki Y, Karasawa K, et al. Analysis of the results of combined therapy for maxillary carcinoma. *Cancer* 1993; 71:2715-2722.
 40. Harrison DFN. Problems in surgical management of neoplasms arising in the paranasal sinuses. *J Laryngol Otol* 1976; 90:69-74.
 41. Larson DL, Christ JE, Jesse RH. Preservation of the orbital contents in cancer of the maxillary sinus. *Arch Otolaryngol* 1982; 108:370-372.
 42. Perry C, Levine PA, Williamson BR, et al. Preservation of the eye in paranasal sinus cancer surgery. *Arch Otolaryngol Head Neck Surg* 1988; 114:632-634.
 43. Graamans K, Slootweg PJ. Orbital exenteration in surgery of malignant neoplasms of the paranasal sinuses. The value of preoperative computed tomography. *Arch Otolaryngol Head Neck Surg* 1989; 115:977-980.
 44. Stern SJ, Geopfert H, Clayman G, et al. Orbital preservation in maxillectomy. *Otolaryngol Head Neck Surg* 1993; 109:111-115.
 45. Boone MLM, Harle TS, Higholt HW, et al. Malignant disease of the paranasal sinuses and nasal cavity. Importance of precise localization of extent of disease. *AJR Am J Roentgenol* 1968; 102:627-636.
 46. Weymuller EA Jr, Reardon EJ, Nash D. A comparison of treatment modalities in carcinoma of the maxillary antrum. *Arch Otolaryngol* 1980; 106:625-629.

XV. NONKERATINIZING CARCINOMA

1. Pilch BZ, Bouquet J, Thompson LDR. Squamous cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours, Pathology and Genetics, Head and Neck Tumours*. Lyon: IARC Press, 2005:15-17.
2. Osborn DA. Nature and behavior of transitional tumors of the upper respiratory tract. *Cancer* 1970; 25:50-60.
3. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histologic types. *Clin Otolaryngol* 1979; 4: 431-456.
4. El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract. A distinct clinicopathologic and molecular disease entity. *Am J Surg Pathol* 2005; 29: 1367-1372.
5. Auerbach MJ, Adair CF, Kardon D, et al. Respiratory epithelial carcinoma: a clinicopathologic study. *Lab Invest* 2002; 82:215A (abstract).
6. Manivel C, Wack MR, Dehner LP. Transitional (cylindrical) cell carcinoma with endodermal sinus tumor-like features of the nasopharynx and paranasal sinuses. Clinicopathologic and immunohistochemical study of two cases. *Arch Pathol Lab Med* 1986; 110:198-202.

7. Franchi A, Moroni M, Massi D, et al. Sinonasal undifferentiated carcinoma, a nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. *Am J Surg Pathol* 2002; 26:1597-1604.
8. Gotte K, Riedel F, Schafer C, et al. Cylindrical cell carcinoma of the paranasal sinuses do not show p53 alterations but loss of heterozygosity at 3p and 17p. *Int J Cancer* 2000; 5: 740-742.

XVI. SINONASAL UNDIFFERENTIATED CARCINOMA

1. Frierson HF Jr, Mills SE, Fechner RE, et al. Sinonasal undifferentiated carcinoma: an aggressive neoplasm, derived from Schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol* 1986; 10:771-779.
2. Frierson HF Jr. Sinonasal undifferentiated carcinoma. In: Barnes L, Eveson JW, Reichart P, et al. eds. *World Health Organization Classification of Tumors. Pathology and Genetics. Head and Neck Tumours*. Lyon: IARC Press, 2005:19.
3. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol* 2002; 15:264-278.
4. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma. Clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. *Adv Anat Pathol* 2005; 12:134-143.
5. Lopategui JR, Gaffey MJ, Frierson HF Jr, et al. Detection of Epstein-Barr viral RNA in sinonasal undifferentiated carcinoma from Western and Asian patients. *Am J Surg Pathol* 1994; 18:391-398.
6. Gallo O, DiLollo S, Graziani P, et al. Detection of Epstein-Barr virus genome in sinonasal undifferentiated carcinoma by use of in situ hybridization. *Otolaryngol Head Neck Surg* 1995; 112:659-664.
7. Jeng Y-M, Sung M-T, Fang C-L, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma. Two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol* 2002; 26:371-376.
8. Cerilli LA, Holst VA, Brandwein MS, et al. Sinonasal undifferentiated carcinoma. Immunohistochemical profile and lack of EBV association. *Am J Surg Pathol* 2001; 25:156-163.
9. Levine PA, Frierson HF Jr, Stewart FM, et al. Sinonasal undifferentiated carcinoma: a destructive and highly aggressive neoplasm. *Laryngoscope* 1987; 97:905-908.
10. Greger V, Schirmacher P, Bohl J, et al. Possible involvement of the retinoblastoma gene in undifferentiated sinonasal carcinoma. *Cancer* 1990; 66:1954-1959.
11. Miyamoto RC, Gleich LL, Biddinger PW, et al. Esthesioneuroblastoma and sinonasal undifferentiated carcinoma: impact of histological grading and clinical staging on survival and prognosis. *Laryngoscope* 2000; 110:1262-1265.
12. Musy PY, Reibel JF, Levine PA. Sinonasal undifferentiated carcinoma: the search for a better outcome. *Laryngoscope* 2002; 112:1450-1455.
13. Rosenthal DI, Barker JL Jr, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation. Patterns of failure according to histologic phenotype. *Cancer* 2004; 101:2567-2573.
14. Rischin D, Porceddu S, Peters L, et al. Promising results with chemoradiation in patients with sinonasal undifferentiated carcinoma. *Head Neck* 2004; 26:435-441.

15. Franchi A, Moroni M, Massi D, et al. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. *Am J Surg Pathol* 2002; 26:1597–1604.
16. Iezzoni JC, Mills SE. "Undifferentiated" small round cell tumors of the sinonasal tract. *Pathology Patterns Reviews*. *Am J Clin Pathol* 2005; 124:(suppl 1):S110–S121.
17. Devaney K, Wenig BM, Abbondanzo SL. Olfactory neuroblastoma and other round cell lesions of the sinonasal tract. *Mod Pathol* 1996; 9:658–663.
18. Enepekides DJ. Sinonasal undifferentiated carcinoma: an update. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13:222–225.
19. Mendenhall WM, Mendenhall CM, Riggs CE Jr, et al. Sinonasal undifferentiated carcinoma. *Am J Clin Oncol* 2006; 29:27–31.
20. Pitman KT, Costantino PD, Lassen LF. Sinonasal undifferentiated carcinoma: current trends in treatment. *Skull Base Surg* 1995; 5:269–272.
4. Kameya T, Shimamoto Y, Adachi I, et al. Neuroendocrine carcinoma of the paranasal sinus. A morphological and endocrinological study. *Cancer* 1980; 45:330–339.
5. Silva EG, Butler JJ, Mackay B, et al. Neuroblastomas and neuroendocrine carcinomas of the nasal cavity. A proposed new classification. *Cancer* 1982; 50:2388–2405.
6. Ordonez NG, Mackay B. Neuroendocrine tumors of the nasal cavity. *Pathol Annu* 1993; 28:77–111.
7. Raychowdhuri RN. Oat-cell carcinoma and paranasal sinuses. *J Laryngol Otol* 1965; 79:253–255.
8. Rejowski JE, Campanella RS, Block LJ. Small cell carcinoma of the nose and paranasal sinuses. *Otolaryngol Head Neck Surg* 1982; 90:516–517.
9. Weiss MD, deFries HO, Taxy JB, et al. Primary small cell carcinoma of the paranasal sinuses. *Arch Otolaryngol* 1983; 109:341–343.
10. Baugh RF, Wolf GT, McClatchey KD. Small cell carcinoma of the head and neck. *Head Neck Surg* 1986; 8:343–354.
11. Soussi AC, Benghiat A, Holgate CS, et al. Neuroendocrine tumours of the head and neck. *J Laryngol Otol* 1990; 104:504–507.
12. Chaudhry MR, Aktar S, Kim DS. Neuroendocrine carcinoma of the ethmoid sinus. *Eur Arch Otorhinolaryngol* 1994; 251:461–463.
13. Pierce ST, Cibull ML, Metcalfe MS, et al. Bone marrow metastases from small cell carcinoma of the head and neck. *Head Neck* 1994; 16:266–271.
14. Perez-Ordóñez B, Caruana SM, Huvos AG, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *Hum Pathol* 1998; 29:826–832.
15. Rosenthal DI, Barker JL Jr, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation. Patterns of failure according to histologic phenotype. *Cancer* 2004; 101:2567–2573.
16. Babin E, Rouleau V, Vedrine PO, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *J Laryngol Otol* 2006; 120:289–297.
17. Mineta H, Miura K, Takebayashi S, et al. Immunohistochemical analysis of small cell carcinoma of the head and neck: a report of four patients and a review of 16 patients in the literature with ectopic hormone production. *Ann Otol Rhinol Laryngol* 2001; 110:76–82.
18. Cheuk W, Chan JKC. Thyroid transcription factor-1 is of limited value in practical distinction between pulmonary and extrapulmonary small cell carcinomas. *Am J Surg Pathol* 2001; 25:545 (letter to editor).
19. Iezzoni JC, Mills SE. "Undifferentiated" small round cell tumors of the sinonasal tract. Differential diagnosis update. *Pathology Patterns Reviews*. *Am J Clin Pathol* 2005; 124:(suppl):S-110–S121.
20. Barnes L, Brandwein M, Som PM. Diseases of the Nasal Cavity, paranasal sinuses and nasopharynx. In: Barnes L ed. *Surgical Pathology of the Head and Neck, Second Edition Revised and Expanded*. New York: Marcel Dekker, 2005:439–555.
21. Perez-Ordóñez B. Neuroendocrine tumours. In: Barnes L, Eveson JW, Reichart P, et al. eds. *World Health Organization Classification of Tumours, Pathology and Genetics, Head and Neck Tumours*. Lyon: IARC Press, 2005:26–27.

XVII. NEUROENDOCRINE CARCINOMA

1. Baugh RF, Wolf GT, Lloyd RV, et al. Carcinoid (neuroendocrine carcinoma) of the larynx. *Ann Otol Rhinol Laryngol* 1987; 96:315–321.
2. Stanley RJ, DeSanto LW, Weiland LH. Oncocytic and oncocytoid carcinoid tumors (well-differentiated neuroendocrine carcinomas) of the larynx. *Arch Otolaryngol Head Neck Surg* 1986; 112:529–535.
3. Wenig BM, Gnepp DR. The spectrum of neuroendocrine carcinomas of the larynx. *Semin Diagn Pathol* 1989; 6:329–350.
4. Gnepp DR. Small cell neuroendocrine carcinoma of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec* 1991; 53:210–219.
5. Benning TL, Vollmer RT, Crain BJ, et al. Neuroendocrine carcinoma of the oral cavity. *Mod Pathol* 1990; 3:631–634.
6. Silva EG, Butler JJ, Mackay B, et al. Neuroblastomas and neuroendocrine carcinomas of the nasal cavity. A proposed new classification. *Cancer* 1982; 50:2238–2405.
7. Ordóñez NG, Mackay B. Neuroendocrine tumors of the nasal cavity. *Pathol Annu* 1993; 28:77–111.
8. Baugh RF, Wolf GT, McClatchey KD. Small cell carcinoma of the head and neck. *Head Neck Surg* 1986; 8:343–354.
9. Taxy JB, Bharani NK, Mills SE, et al. The spectrum of olfactory neural tumors. A light microscopic, immunohistochemical and ultrastructural analysis. *Am J Surg Pathol* 1986; 10:687–695.
10. Barnes L, Eveson JW, Reichart P, et al. *World Health Organization Classification of Tumours, Pathology and Genetics, Head and Neck Tumours*. Lyon: IARC Press, 2005.

XVIII. SMALL CELL NEUROENDOCRINE CARCINOMA

1. Gnepp DR. Small cell neuroendocrine carcinoma of the larynx. A critical review of the literature. *J Otorhinolaryngol Relat Spec* 1991; 53:210–219.
2. Koss LG, Spiro RH, Hajdu S. Small cell (oat cell) carcinoma of minor salivary gland origin. *Cancer* 1972; 30:737–741.
3. Gnepp DR, Wick MR. Small cell carcinoma of the major salivary glands. An immunohistochemical study. *Cancer* 1990; 66:185–192.

XIX. LYMPHOEPITHELIAL CARCINOMA

1. Lopategui JR, Gaffey MJ, Frierson HF Jr, et al. Detection of Epstein-Barr viral RNA in sinonasal undifferentiated carcinoma from Western and Asian patients. *Am J Surg Pathol* 1994; 18:391–398.

2. Leung SY, Yuen ST, Chung LP, et al. Epstein-Barr virus is present in a wide histologic spectrum of sinonasal carcinomas. *Am J Surg Pathol* 1995; 19:994-1001.
3. Dubey P, Ha CS, Ang KK, et al. Nonnasopharyngeal lymphoepithelioma of the head and neck. *Cancer* 1998; 82:1556-1562.
4. Zong Y, Liu K, Zong B, et al. Epstein-Barr virus infection of sinonasal lymphoepithelial carcinoma in Guangzhou. *Chin Med J (Engl)* 2001; 114:132-136.
5. Franchi A, Moroni M, Massi D. Sinonasal undifferentiated carcinoma, nasopharyngeal type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin pattern. *Am J Surg Pathol* 2002; 26:1597-1604.
6. Jeng Y-M, Sung M-T, Fang C-L, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma. Two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol* 2002; 26:371-376.
7. Hajjiannou JK, Kyrmizakis E, Datseris G, et al. Nasopharyngeal-type undifferentiated carcinoma (lymphoepithelioma) of paranasal sinuses: Rare case and literature review. *J Otolaryngol* 2006; 35:147-151.
14. Acheson ED, Cowdell RH, Hadfield E, et al. Nasal cancer in woodworkers in the furniture industry. *Br Med J* 1968; 2:587-596.
15. Brinton LA, Blot WJ, Stone BJ, et al. A death certificate analysis of nasal cancer among furniture workers in North Carolina. *Cancer Res* 1977; 37:3473-3474.
16. Ironside P, Matthews J. Adenocarcinoma of the nose and paranasal sinuses in woodworkers in the state of Victoria, Australia. *Cancer* 1975; 36:1115-1121.
17. Cecchi F, Buiatti E, Kriebel D, et al. Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy. *Br J Ind Med* 1980; 37:222-225.
18. Klintenberg C, Olofsson J, Hellquist H, et al. Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. *Cancer* 1984; 54:482-488.
19. Kleinsasser O, Schroeder H-G. Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. *Arch Otorhinolaryngol* 1988; 245:1-15.
20. Kwachi I, Pearce N, Fraser J. A New Zealand cancer registry-based study of cancer in woodworkers. *Cancer* 1989; 64:2609-2613.
21. Shimizu H, Hozawa J, Saito H, et al. Chronic sinusitis and woodworking as risk factors for cancer of the maxillary sinus in northeast Japan. *Laryngoscope* 1989; 99:58-61.
22. Luce D, Luclerc A, Morcet J-F, et al. Occupational risk factors for sinonasal cancer: a case-control study in France. *Am J Ind Med* 1992; 21:163-175.
23. Nunez F, Suarez C, Alvarez I, et al. Sino-nasal adenocarcinoma: epidemiological and clinicopathological study of 34 cases. *J Otolaryngol* 1993; 22:86-90.
24. Mohtashamipour E, Norpoth K, Luhmann F. Cancer epidemiology of woodworking. *J Cancer Res Clin Oncol* 1989; 115:503-515.
25. Urso C, Ninu MB, Franchi A, et al. Intestinal-type adenocarcinoma of the sinonasal tract: clinicopathologic study of 18 cases. *Tumori* 1993; 79:205-210.
26. Nylander LA, Dement JM. Carcinogenic effects of wood dust: review and discussion. *Am J Ind Med* 1993; 24:619-647.
27. Leclerc A, Cortes MM, Gerin M, et al. Sinonasal cancer and wood dust exposure: results from a case-control study. *Am J Epidemiol* 1994; 140:340-349.
28. Acheson ED, Cowdell RH, Jolles B. Nasal cancer in the furniture and boot and shoe manufacturing industries. *Prev Med* 1976; 5:295-315.
29. Rousch GC. Epidemiology of cancer of the nose and paranasal sinuses. Current concepts. *Head Neck Surg* 1979; 2:3-11.
30. Hadfield EH. A study of adenocarcinoma of the paranasal sinuses in woodworkers in the furniture industry. *Ann R Coll Surg Engl* 1970; 46:301-319.
31. Wilhelmsson B, Lundh B. Nasal epithelium in woodworkers in the furniture industry. A histologic and cytological study. *Acta Otolaryngol* 1984; 98:321-334.
32. Spiro RH, Koss LG, Hajdu SI, et al. Tumors of minor salivary origin. A clinicopathologic study of 492 cases. *Cancer* 1973; 31:117-129.
33. Lopez JI, Perez A. Pharyngeal adenocarcinoma with intestinal features. *J Laryngol Otol* 1990; 104:900-902.
34. Ellis GL, Auclair PL. Mucinous adenocarcinoma. In: *Atlas of Tumor Pathology. Tumors of the Salivary Glands, Third Series*. Washington, DC: Armed Forces Institute of Pathology, 1996:349-352.

XX. INTESTINAL-TYPE ADENOCARCINOMA

1. Lewis JS, Castro EB. Cancer of the nasal cavity and paranasal sinuses. *J Laryngol Otol* 1972; 86:255-262.
2. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. *Clin Otolaryngol* 1979; 4:431-456.
3. Weber AL, Stanton AC. Malignant tumors of the paranasal sinuses: radiologic, clinical, and histopathologic evaluation of 200 cases. *Head Neck Surg* 1984; 6:761-776.
4. Sanchez-Casis G, Devine KD, Weiland LH. Nasal adenocarcinomas that closely simulate colonic carcinomas. *Cancer* 1971; 28:714-720.
5. Schmid KO, Aubock L, Albegger K. Endocrine-amphicrine enteric carcinoma of the nasal mucosa. *Virchows Arch A Pathol Anat Histol* 1979; 383: 329-343.
6. Mills SE, Fechner RE, Cantrell RW. Aggressive sinonasal lesion resembling normal intestinal mucosa. *Am J Surg Pathol* 1982; 6:803-909.
7. Batsakis JG, Mackay B, Ordonez NG. Enteric-type adenocarcinoma of the nasal cavity. An electron microscopic and immunocytochemical study. *Cancer* 1984; 54:855-860.
8. Gamez-Araujo JJ, Ayala AG, Guillaumondegui O. Mucinous adenocarcinomas of nose and paranasal sinuses. *Cancer* 1975; 36:1100-1105.
9. Jarvi O. Heterotopic tumors with an intestinal mucous membrane structure in the nasal cavity. *Acta Otolaryngol* 1945; 33:471-485.
10. Simard LC, Jean A. Adenocarcinoma with argentaffin cells of the nasal cavity, giving widespread metastases. *Cancer* 1953; 6:699-703.
11. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Am J Surg Pathol* 1986; 10:192-202.
12. Franchi A, Santucci M, Wenig BM. Adenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al. eds. *World Health Organization Classification of Tumours, Pathology and Genetics, Head and Neck Tumours*. Lyon: IARC Press, 2005:20-23.
13. Macbeth R. Malignant disease of the paranasal sinuses. *J Laryngol Otol* 1965; 79:592-612.

35. Salassa JR, McDonald TJ, Wieland LH. "Colonic type" adenocarcinoma of the nasal cavity and paranasal sinuses. *Otolaryngol Head Neck Surg* 1980; 88:133-135.
36. Boor A, Dudrikova K, Kavecansky V, et al. Intestinal-type sinonasal adenocarcinoma: a sporadic case. *J Laryngol Otol* 1996; 110:805-810.
37. Alessi DM, Trapp TK, Fu YS, et al. Nonsalivary sinonasal adenocarcinoma. *Arch Otolaryngol Head Neck Surg* 1988; 114:996-999.
38. Orvidas LJ, Lewis JE, Weaver AL, et al. Adenocarcinoma of the nose and paranasal sinuses: a retrospective study of diagnosis, histologic characteristics, and outcome in 24 patients. *Head Neck* 2005; 27:370-375.
39. Franchi A, Gallo O, Santucci M. Clinical relevance of the histological classification of sinonasal intestinal-type adenocarcinomas. *Hum Pathol* 1999; 30:1140-1145.
40. Gnepp DR, Heffner DK. Mucosal origin of sinonasal tract adenomatous neoplasms. *Mod Pathol* 1989; 2:365-371.
41. Kleinsasser O, Schroeder HG, Mayer-Brix J. Preinvasive stages of adenocarcinoma of the nose after exposure to wood dust. *Eur Arch Otorhinolaryngol* 1991; 248:222-229.
42. Cheng H, Leblond CP. Origin, differentiation and renewal of four main epithelial types in the mouse small intestine. V. Unitarian theory of the origin of the four epithelial cell types. *Am J Anat* 1974; 141:537-561.
43. Kirkland SC. Clonal origin of columnar, mucous, and endocrine cell lineages in human colorectal epithelium. *Cancer* 1988; 61:1359-1363.
44. McKinney CD, Mills SE, Franquemont DW. Sinonasal intestinal-type adenocarcinoma: Immunohistochemical profile and comparison with colonic adenocarcinoma. *Mod Pathol* 1995; 8:421-426.
45. Kennedy MT, Jordan RCK, Berean KW, et al. Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma. *J Clin Pathol* 2004; 57:932-937.
46. Ortiz-Rey JA, Alvarez C, Miguel PS, et al. Expression of CDX2, cytokeratins 7 and 20 in sinonasal-type adenocarcinoma. *Appl Immunohistochem Mol Morphol* 2005; 13:142-146.
47. Resto VA, Krane JF, Faquin WC, et al. Immunohistochemical distinction of intestinal-type sinonasal adenocarcinoma from metastatic adenocarcinoma of intestinal origin. *Ann Otol Rhinol Laryngol* 2006; 115:59-64.
48. Franchi A, Massi D, Palombra, et al. CDX-2, cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinoma of the sinonasal tract. *Virchows Arch* 2004; 445:63-67. [Epub 2004, Jun 3].
49. Amre R, Ghali V, Elmberger G, et al. Sinonasal "intestinal-type" adenocarcinoma (SNITAC): an immunohistochemical (IHC) of 22 cases. *Mod Pathol* 2004; 17(suppl 1):221A (abstract).
50. Bashir AA, Robinson RA, Benda JA, et al. Sinonasal adenocarcinoma: immunohistochemical marking and expression of oncoproteins. *Head Neck* 2003; 25:763-771.
51. Abecasis J, Viana G, Pissarra C, et al. Adenocarcinoma of the nasal cavity and paranasal sinuses: a clinicopathological and immunohistochemical study of 14 cases. *Histopathology* 2004; 45:254-259.
52. Choi H-R, Sturgis EM, Rashid A, et al. Sinonasal adenocarcinoma: evidence for histogenetic divergence of the enteric and nonenteric phenotypes. *Hum Pathol* 2003; 34:1101-1107.
53. Cathro HP, Mills SE. Immunophenotypic differences between intestinal-type and low-grade papillary sinonasal adenocarcinomas. An immunohistochemical study of 22 cases utilizing CDX2 and MUC2. *Am J Surg Pathol* 2004; 28:1026-1032.
54. Yom SS, Rashid A, Rosenthal DI, et al. Genetic analysis of sinonasal adenocarcinoma phenotypes: distinct alterations of histologic significance. *Mod Pathol* 2005; 18:315-319.
55. Perez P, Dominguez O, Gonzalez S, et al. Ras gene mutations in ethmoid sinus adenocarcinoma. Prognostic implications. *Cancer* 1999; 86:255-264.
56. Perrone F, Oggionni M, Birindelli S, et al. TP53, P14^{ARF}, P16^{INK4A}, and H-RAS gene molecular analysis in intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Int J Cancer* 2003; 105:196-203.
57. Saber AT, Nielsen LR, Dictor M, et al. K-ras mutations in sinonasal adenocarcinomas in patients occupationally exposed to wood or leather dust. *Cancer Lett* 1998; 126:59-65.
58. Perez-Ordonez B, Huynh NN, Berean KW, et al. Expression of mismatch repair proteins, B catenin and E cadherin in intestinal-type adenocarcinoma. *J Clin Pathol* 2004; 57:1080-1083.
59. Wu TT, Barnes L, Bakker A, et al. K-ras-2 and p53 genotyping of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Mod Pathol* 1996; 9:199-204.
60. Ariz M, Llorenta JL, Alvarez-Marcas C, et al. Comparative genomic hybridization in primary sinonasal adenocarcinomas. *Cancer* 2004; 100:335-341.
61. Bernstein JM, Montgomery WW, Balogh K. Metastatic tumor to the maxilla and paranasal sinuses. *Laryngoscope* 1966; 76:621-650.
62. Owa AO, Gallimore AP, Ajulo SO, et al. Metastatic adenocarcinoma of the ethmoids in a patient with previous gastric adenocarcinoma: a case report. *J Laryngol Otol* 1995; 109:759-751.
63. Zhang PJ, Shah M, Spiegel GW, et al. Cytokeratin 7 immunoreactivity in rectal adenocarcinomas. *Appl Immunohistochem Mol Morphol* 2003; 11:306-310.

XXI. NON-INTESTINAL-TYPE ADENOCARCINOMA

1. Heffner DK, Hyams VJ, Hauck KW, et al. Low-grade adenocarcinoma of the nasal cavity and paranasal sinuses. *Cancer* 1982; 50:312-322.
2. Neto AG, Pineda-Daboin K, Luna MA. Sinonasal tract seromucinous adenocarcinoma: a report of 12 cases. *Ann Diagn Pathol* 2003; 7:154-159.
3. Skalova A, Cardesa A, Leivo I, et al. Sinonasal tubulopapillary low-grade adenocarcinoma. Histopathological, immunohistochemical and ultrastructural features of a poorly recognized entity. *Virchow Arch* 2003; 443:152-158.
4. Luna MA. Sinonasal tubulopapillary low-grade adenocarcinoma. A specific diagnosis or just another seromucinous adenocarcinoma? *Adv Anat Pathol* 2005; 12:109-115.
5. Cathro HP, Mills SE. Immunophenotypic differences between intestinal-type and low-grade papillary sinonasal adenocarcinomas. An immunohistochemical study of 22 cases utilizing CDX2 and MUC2. *Am J Surg Pathol* 2004; 28:1026-1032.
6. Amre R, Ghali V, Elmberger G, et al. Sinonasal "intestinal-type" adenocarcinoma (SNITAC): an immunohistochemical study of 22 cases. *Mod Pathol* 2004; 17(suppl 1):221 A (abstract).

XXII. SALIVARY-TYPE NEOPLASMS

1. Heffner DK. Sinonasal and laryngeal salivary gland lesions. In: Ellis GL, Auclair PL, Gnepp DR, eds.

- Surgical Pathology of the Salivary Glands, Major Problems in Pathology. Philadelphia: WB Saunders, 1991: 544-559.
2. Gnepp DR, Heffner DK. Mucosal origin of sinonasal tract adenomatous neoplasms. *Mod Pathol* 1989; 2:365-371.
 3. Compagno J, Wong RT. Intranasal tumors (pleomorphic adenomas). A clinicopathologic study of 40 cases. *Am J Clin Pathol* 1977; 68:213-218.
 4. Narozny W, Kuczkowski J, Mikaszewski B. Pleomorphic adenoma of the nasal cavity: clinical analysis of 8 cases. *Am J Otolaryngol* 2005; 26:218.
 5. Lee KC, Chan JKC, Chong YW. Ossifying pleomorphic adenoma of the maxillary antrum. *J Laryngol Otol* 1992; 106:50-52.
 6. Prager DA, Weiss MH, Buchalter WL, et al. Pleomorphic adenoma of the nasal cavity. *Ann Otol Rhinol Laryngol* 1991; 100:600.
 7. Lam PWY, Chan JKC, Sin V-C. Nasal pleomorphic adenoma with skeletal muscle differentiation: potential misdiagnosis as rhabdomyosarcoma. *Hum Pathol* 1997; 28:1299-1302.
 8. Cho KJ, El-Naggar AK, Mahanupab P, et al. Carcinoma ex-pleomorphic adenoma of the nasal cavity: a report of two cases. *J Laryngol Otol* 1995; 109:677-679.
 9. Buchanan JA, Krolls SO, Sneed WF. Oncocytoma in the nasal vestibule. *Otolaryngol Head Neck Surg* 1988; 99:63-65.
 10. Martin H, Janda J, Behrbohm H. Locally invasive oncocytoma of the nasal cavity. *Zentralbl Allg Pathol* 1990; 136:703-706.
 11. Forster C, Ostertag H. Oncocytoma of the nose. A case report and review of the literature. *Pathologe* 1995; 16: 431-433.
 12. Comin CE, Dini M, Russo GL. Oncocytoma of the nasal cavity: report of a case and review of the literature. *J Laryngol Otol* 1997; 111:671-673.
 13. Nayak DR, Pillai S, Balakrishnan R, et al. Malignant oncocytoma of the nasal cavity: a case report. *Am J Otolaryngol* 1999; 20:323-327.
 14. Ozolek JA, Hunt JL. Immunohistochemical staining characteristics of oncocytomas of major salivary gland: comparison to conventional renal cell carcinoma. *Mod Pathol* 2004; 17:230A (abstract).
 15. Neto AG, Pineda-Daboin K, Spencer ML, et al. Sinonasal acinic cell carcinoma: a clinicopathologic study of four cases. *Head Neck* 2005; 27:603-607.
 16. Konno A, Ishikawa K, Numata T, et al. Analysis of factors affecting long-term treatment results of adenoid cystic carcinoma of the nose and paranasal sinuses. *Acta Otolaryngol (Stockh)* 1998; suppl 537:67-74.
 17. Kim GE, Park HC, Keum KC, et al. Adenoid cystic carcinoma of the maxillary antrum. *Am J Otolaryngol* 1999; 20:77-85.
 18. Naficy S, Disher MJ, Esclamado RM. Adenoid cystic carcinoma of the paranasal sinuses. *Am J Rhinol* 1999; 13: 311-314.
 19. Wiseman SM, Orner JB, Popat SR, et al. Adenoid cystic carcinoma of the paranasal sinuses or nasal cavity: a 40-year review of 35 cases. *Ear Nose Throat J* 2002; 81:510-517.
 20. Dulguerov P, Jacobson MS, Allal AA, et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001; 92:3012-3029.
 21. Thompson CDR, Nelson BL. Sinonasal tract mucoepidermoid carcinoma: A clinicopathologic and immunophenotypic study of 19 cases. *Mod Pathol* 2005; 18:218A (abstract).
 22. Begin LR, Rochon L, Frenkiel S. Spindle cell myoepithelioma of the nasal cavity. *Am J Surg Pathol* 1991; 15:184-190.
 23. Jin KL, Ding CN, Chu Q. Epithelial-myoepithelial carcinoma arising in the nasal cavity: a case report and review of the literature. *Pathology* 1999; 31:148-151.
 24. Lloreta J, Serrano S, Corominas JM, et al. Polymorphous low-grade adenocarcinoma arising in the nasal cavities with an associated undifferentiated carcinoma. *Ultrastruct Pathol* 1995; 19:365-370.
 25. Fonseca I, Soares J. Basal cell adenocarcinoma of minor salivary and seromucinous glands of the head and neck. *Semin Diagn Pathol* 1996; 13:128-137.
 26. Kuo T-T, Tsang N-M. Salivary gland type nasopharyngeal carcinoma. A histologic, immunohistochemical, and Epstein-Barr virus study of 15 cases including a psammomatous mucoepidermoid carcinoma. *Am J Surg Pathol* 2001; 25:80-86.

XXIII. MALIGNANT MELANOMA

1. Harris TJ, Hinckley DM. Melanoma of the head and neck in Queensland. *Head Neck Surg* 1983; 5:197-203.
2. Thorn M, Adami H-O, Ringborg U, et al. The association between anatomic site and survival in malignant melanoma. An analysis 12,353 cases from the Swedish Cancer Registry. *Eur J Cancer Clin Oncol* 1989; 25:483-491.
3. Fisher SR. Cutaneous malignant melanoma of the head and neck. *Laryngoscope* 1989; 99:822-836.
4. Urist MM, Karnell LH. The National Cancer Data Base. Report on melanoma. *Cancer* 1994; 74:782-788.
5. Garbe C, Buttner P, Bertz J, et al. Primary cutaneous melanoma. Identification of prognostic groups and estimation of individual prognosis for 5093 patients. *Cancer* 1995; 75:2484-2491.
6. Conley JJ. Melanomas of the mucous membranes of the head and neck. *Laryngoscope* 1989; 99:1248-1254.
7. Moore ES, Martin H. Melanoma of the upper respiratory tract and oral cavity. *Cancer* 1955; 8:1167-1176.
8. Allen AL, Spitz S. Malignant melanoma. *Cancer* 1953; 6:1-45.
9. Lund V. Malignant melanoma of the nasal cavity and paranasal sinuses. *J Laryngol Otol* 1982; 96:347-355.
10. Lederman M. Tumours of the upper jaw: natural history and treatment. *J Laryngol Otol* 1982; 96:347-355.
11. Jackson RT, Fitz-Hugh GS, Constable WC. Malignant neoplasms of the nasal cavities and paranasal sinuses: (a retrospective study). *Laryngoscope* 1977; 87:726-736.
12. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. *Clin Otolaryngol* 1979; 4:431-456.
13. Gadeberg CC, Hjelm-Hansen M, Sogaard H, et al. Malignant tumours of the paranasal sinuses and nasal cavity. A series of 180 patients. *Acta Radiol Oncol* 1984; 23:181-187.
14. Spiro JD, Soo KC, Spiro RH. Nonsquamous cell malignant neoplasms of the nasal cavities and paranasal sinuses. *Head Neck* 1995; 17:114-118.
15. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review. Bethesda, MD: National Cancer Institute, 2003.
16. Carlson JA, Slominski A, Linette GP, et al. Malignant melanoma 2003. Predisposition, diagnosis, prognosis and staging. *Am J Clin Pathol* 2003; 120(suppl 1): S101-S127.
17. Rigel DS. Epidemiology and prognostic factors in malignant melanoma. *Ann Plast Surg* 1992; 28:7-8.
18. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base Report on Cutaneous and Noncutaneous

- melanoma. A summary of 84,836 cases from the past decade. *Cancer* 1998; 83:1664-1678.
19. Zak FG, Lawson W. The presence of melanocytes in the nasal cavity. *Ann Otol Rhinol Laryngol* 1974; 83:515-519.
 20. Thompson LDR, Wieneke JA, Miettinen M. Sinonasal tract and nasopharyngeal melanomas. A clinicopathologic study of 115 cases with a proposed staging system. *Am J Surg Pathol* 2003; 27:594-611.
 21. Kousseff BG. The genetics of malignant melanomas. *Ann Plast Surg* 1992; 28:11-13.
 22. Hoffman S, Yohn J, Robinson W, et al. Melanoma: 1. Clinical characteristics. *Hosp Pract (Ed)* 1994; 29:37-47.
 23. Lewis MG, Martin JAM. Malignant melanoma of the nasal cavity in Ugandan Africans. Relationship of ectopic pigmentation. *Cancer* 1967; 20:1699-1705.
 24. Cove H. Melanosis, melanocytic hyperplasia, and primary malignant melanoma of the nasal cavity. *Cancer* 1979; 44:1424-1433.
 25. Hofbauer GFL, Boni R, Simmen D, et al. Histological, immunological and molecular features of a nasal mucosa primary melanoma associated with a nasal melanosis. *Melanoma Res* 2002; 12:77-82.
 26. Holdcraft J, Gallagher JC. Malignant melanoma of the nasal and paranasal sinus mucosa. *Ann Otol Rhinol Laryngol* 1969; 78:1-16.
 27. Freedman HM, DeSanto LW, Devine KD, et al. Malignant melanoma of the nasal cavity and paranasal sinuses. *Arch Otolaryngol* 1973; 97:322-325.
 28. Conley J, Pack GT. Melanoma of the mucous membranes of the head and neck. *Arch Otolaryngol* 1974; 99:315-319.
 29. Eneroth C-M, Lundberg C. Mucosal malignant melanoma of the head and neck. With special reference to cases having a prolonged clinical course. *Acta Otolaryngol* 1975; 80:452-458.
 30. Shah JP, Huvos AG, Strong EW. Mucosal melanomas of the head and neck. *Am J Surg* 1977; 134:531-535.
 31. Snow GB, Van Der Esch EP, Van Slooten EA. Mucosal melanomas of the head and neck. *Head Neck Surg* 1978; 1:24-30.
 32. Bethelsen A, Andersen AP, Jensen TS, et al. Melanomas of the mucosa in the oral cavity and the upper respiratory passages. *Cancer* 1984; 54:907-912.
 33. Blatchford SJ, Koopmann CF Jr, Coulthard SW. Mucosal melanoma of the head and neck. *Laryngoscope* 1986; 96:929-934.
 34. Panje WR, Moran WJ. Melanoma of the upper aerodigestive tract: a review of 21 cases. *Head Neck Surg* 1986; 96:929-934.
 35. Trapp TK, Fu Y-S, Calcaterra TC. Melanoma of the nasal and paranasal sinus mucosa. *Arch Otolaryngol Head Neck Surg* 1987; 113:1086-1089.
 36. Suen JY, Median J, Westbrook KC. Nasal septal melanoma. *Head Neck Surg* 1988; 10:432-435.
 37. Going JJ, Kean DM. Malignant melanoma of the nasal cavity. *J Laryngol Otol* 1989; 103:231-233.
 38. Gilligan D, Slevin NJ. Radical radiotherapy for 28 cases of mucosal melanoma in the nasal cavity and sinuses. *Br J Radiol* 1991; 64:1147-1150.
 39. Franquemont DW, Mills SE. Sinonasal malignant melanoma. A clinicopathologic and immunohistochemical study of 14 cases. *Am J Clin Pathol* 1991; 96:689-697.
 40. Stern SJ, Guillaumondegui OM. Mucosal melanoma of the head and neck. *Head Neck* 1991; 96:689-697.
 41. Guzzo M, Grandi C, Licitra L, et al. Mucosal malignant melanoma of head and neck: forty-eight cases treated at Istituto Nazionale Tumori of Milan. *Eur J Surg Oncol* 1993; 19:316-319.
 42. Thompson AC, Morgan DAL, Bradley PJ. Malignant melanoma of the nasal cavity and paranasal sinuses. *Clin Otolaryngol* 1993; 18:34-36.
 43. Kingdom TT, Kaplan MJ. Mucosal melanoma of the nasal cavity and paranasal sinuses. *Head Neck* 1995; 17:184-189.
 44. Huntrakoon M, Nyongo AO. Primary malignant melanoma of the nasal cavity: report of two cases with emphasis on histogenesis. *Am J Surg Pathol* 1989; 2:59-66.
 45. Loree TR, Mullins AP, Spellman J, et al. Head and neck mucosal melanoma: a 32-year review. *Ear Nose Throat J* 1999; 78:372-375.
 46. Brandwein MS, Rothstein A, Lawson W, et al. Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. *Arch Otolaryngol Head Neck Surg* 1997; 123:290-296.
 47. Prasad ML, Patel SG, Huvos AG, et al. Primary mucosal melanoma of the head and neck. A proposal for micro-staging localized, stage I (lymph node-negative) tumors. *Cancer* 2004; 100:1657-1664.
 48. Manolidis S, Donald PJ. Malignant mucosal melanoma of the head and neck. Review of the literature and report of 14 patients. *Cancer* 1997; 80:1373-1386.
 49. Billinger KR, Wang MB, Sercarz JA, et al. Clinical and pathologic distinction between primary and metastatic mucosal melanoma of the head and neck. *Otolaryngol Head Neck Surg* 1995; 112:700-706.
 50. Prasad ML, Patel SG, Busam KJ. Primary mucosal desmoplastic melanoma of the head and neck. *Head Neck* 2004; 26:373-377.
 51. Prasad ML, Jungbluth AA, Iversen K, et al. Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. *Am J Surg Pathol* 2001; 25:782-787.
 52. Van Dijk M, Sprenger S, Rombout P, et al. Distinct chromosomal aberrations in sinonasal mucosa melanoma as detected by comparative genomic hybridization. *Genes Chromosomes Cancer* 2003; 36:151-158.
 53. Curtin JA, Fridlyand J, Kagershita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005; 353:2135-2147.
 54. Nakleh RE, Wick MR, Rocamora A, et al. Morphologic diversity in malignant melanomas. *Am J Clin Pathol* 1990; 93:731-740.
 55. Change ES, Wick MR, Swanson PE, et al. Metastatic malignant melanoma with "rhabdoid" features. *Am J Clin Pathol* 1994; 102:426-431.
 56. Das Gupta T, Brasfield R. Metastatic melanoma: a clinicopathological study. *Cancer* 1964; 17:1323-1339.
 57. Bernstein JM, Montgomery WW, Balogh K Jr. Metastatic tumors to the maxilla, nose and paranasal sinuses. *Laryngoscope* 1966; 76:621-650.
 58. Henderson LT, Robbins T, Weitzner S. Upper aerodigestive tract metastases in disseminated malignant melanoma. *Arch Otolaryngol Head Neck Surg* 1986; 112:659-663.
 59. Bizon JG, Newman RK. Metastatic melanoma to the ethmoid sinus. *Arch Otolaryngol Head Neck Surg* 1986; 112:664-667.
 60. Billings KR, Wang MB, Sercarz JA, et al. Clinical and pathologic distinction between primary and metastatic mucosal melanoma of the head and neck. *Otolaryngol Head Neck Surg* 1995; 112:700-706.
 61. Einhorn LH, Burgess MA, Vallejos C. Prognostic correlations and response to treatment in advanced metastatic malignant melanoma. *Cancer Res* 1974; 34:1995-2004.
 62. Patel JK, Didolkar MS, Pickren JW, et al. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. *Am J Surg* 1978; 135:807-810.

63. Harwood AR, Lawson VG. Radiation therapy for melanomas of the head and neck. *Head Neck Surg* 1982; 4:468-474.
64. Trottie A, Peters LJ. Role of radiotherapy in the primary management of mucosal melanoma of the head and neck. *Semin Surg Oncol* 1993; 9:246-250.
65. Medina JE, Ferlito A, Pellitteri PK, et al. Current management of mucosal melanoma of the head and neck. *J Surg Oncol* 2003; 83:116-123.
66. Mendenhall WM, Amdur RJ, Hinerman RW, et al. Head and neck mucosal melanoma. *Am J Clin Oncol* 2005; 28:626-630.
67. Harrison DFS. Malignant melanomata arising in the nasal mucous membrane. *J Laryngol Otol* 1976; 90:993-1005.
68. Helidonis ES, Myers EN, Barnes EL Jr. Metastasis of malignant melanoma of the nasal mucosa to the small intestine. *Laryngoscope* 1976; 86:1734-1737.
69. Lee Y-TN. Malignant melanoma: pattern of metastasis. *CA Cancer J Clin* 1980; 30:137-142.
70. Patel SG, Prasad ML, Eserig M, et al. Primary mucosal malignant melanoma of the head and neck. *Head Neck* 2002; 24:247-257.
14. Huang DP, Ho HC, Henle G, et al. Presence of EBNA in nasopharyngeal carcinoma and control tissues related to EBV serology. *Int J Cancer* 1978; 22:266-274.
15. Hording U, Nielsen HW, Duagaard S, et al. Human papillomavirus types 11 and 16 detected in nasopharyngeal carcinomas by the polymerase chain reaction. *Laryngoscope* 1996; 104:99-102.
16. Punwaney R, Brandwein MS, Zhang DY, et al. Human papillomavirus may be common within nasopharyngeal carcinoma of Caucasian Americans: investigation of Epstein-Barr virus and human papillomavirus in Eastern and Western nasopharyngeal carcinoma using ligation-dependent polymerase chain reaction. *Head Neck* 1999; 21:21-29.
17. Nam J-M, McLaughlin JK, Blot WJ. Cigarette smoking, alcohol, and nasopharyngeal carcinoma: a case-control study. *J Natl Cancer Inst* 1992; 84: 619-622.
18. Vaugh TL, Strader C, Davis S, et al. Formaldehyde and cancer of the pharynx, sinus and nasal cavity: II. Residential exposures. *Int J Cancer* 1986; 38(5):685-688.
19. Henderson BE, Louie E, Soohoo J, et al. Risk factors associates with nasopharyngeal carcinoma. *N Engl J Med* 1976; 295:1101-1106.
20. Lin TM, Yang CS, Tu SM, et al. Interaction of factors associated with cancer of the nasopharynx. *Cancer* 1979; 44:1419-1423.
21. Jennel D, Hubert A, de Vathaire F, et al. Diet, living conditions and nasopharyngeal carcinoma in Tunisia – a case-control study. *Int J Cancer* 1990; 46:421-425.
22. Hsu M-M, Tu S-M. Nasopharyngeal carcinoma in Taiwan. Clinical manifestations and results of therapy. *Cancer* 1983; 52:362-368.
23. Gustafson RO, Neel HB III. Cancer of the nasopharynx. In: Myers EN, Suen JY, eds. *Cancer of the Head and Neck*, 2nd ed. New York: Churchill-Livingstone 1989:495-508.
24. Dickson RL. Nasopharyngeal carcinoma. An evaluation of 209 patients. *Laryngoscope* 1981; 91:333-354.
25. Sham JST, Choy D. Prognostic factors of nasopharyngeal carcinoma. A review of 759 patients. *Br J Radiol* 1990; 63: 51-58.
26. Dickson RL, Flores AD. Nasopharyngeal carcinoma: an evaluation of 134 patients treated between 1971-1980. *Laryngoscope* 1985; 95:276-283.
27. Qin P, Hu MY, Yan J, et al. Analysis of 1379 patients with nasopharyngeal carcinoma treated by radiation. *Cancer* 1988; 61:1117-1124.
28. Huang T-B. Cancer of the nasopharynx in childhood. *Cancer* 1990; 66:968-971.
29. Singh W. Nasopharyngeal carcinoma in Caucasian children. A 25-year study. *J Laryngol Otol* 1987; 101: 1248-1253.
30. Sham JST, Poon YF, Wei WI, et al. Nasopharyngeal carcinoma in young patients. *Cancer* 1990; 65:2606-2610.
31. Hawkins EP, Krischer JT, Smith BE, et al. Nasopharyngeal carcinomas in children—a retrospective review and demonstration of Epstein-Barr genome in tumor cell cytoplasm: a report of the Pediatric Oncology Group. *Hum Pathol* 1990; 21:805-810.
32. Mertens R, Granzen B, Lassay L, et al. Nasopharyngeal carcinoma in childhood and adolescence. Concept and preliminary results of the cooperative GPOH Study NPC-91. *Cancer* 1997; 80:951-959.
33. Marks JE, Phillips JL, Menek HR. The National Cancer Data Base Report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. *Cancer* 1998; 83:582-588.
34. Skinner DW, van Hassett CA, Tsao SY. Nasopharyngeal carcinoma: modes of presentation. *Ann Otol Rhinol Laryngol* 1991; 100:544-551.

XXIV. NASOPHARYNGEAL CARCINOMA

1. World Health Organization Classification of Tumours, Pathology and Genetics. Head and Neck Tumours. Barnes L, Eveson JW, Reichart P, et al. eds. Lyon:IARC Press, 2005.
2. Adams WS. The transverse dimensions of the nasopharynx in child and adults with observations on its contractile functions. *J Laryngol* 1958; 72:465-471.
3. Lanier A, Bender T, Talbot M, et al. Nasopharyngeal carcinoma in Alaskan Eskimos, Indians, and Aleuts: a review of cases and study of Epstein-Barr virus, HLA, and environmental risk factors. *Cancer* 1980; 46:2100-2106.
4. Gustafson RO, Neel HB III. Cancer of the nasopharynx. In: Myers EN, Suen JY, eds. *Cancer of the Head and Neck*, 2nd edition. New York: Churchill-Livingstone 1989: 495-508.
5. Doll R, Muir C, Waterhouse J. Cancer incidence in five continents. *UICC Monogr Ser* 1970, 2: 334-338.
6. Buell P. The effect of migration on the risk of nasopharyngeal cancer among Chinese. *Cancer Res* 1974; 34: 1189-1191.
7. Dickson RL. Nasopharyngeal carcinoma: an evaluation of 209 patients. *Laryngoscope* 1981; 91:333-354.
8. Goldsmith DB, West TM, Morton R. HLA associations with nasopharyngeal carcinoma in Southern Chinese: a meta-analysis. *Clin Otolaryngol* 2002; 27:61-67.
9. Loh KS, Goh BC, Lu J. Familial nasopharyngeal carcinoma in a cohort of 200 patients. *Arch Otolaryngol Head Neck Surg* 2006; 132:82-85.
10. Armstrong RW, Armstrong MJ, Yu MC, et al. Salted fish and inhalants as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. *Cancer Res* 1983; 43:2967-2970.
11. Yu MC, Ho JHC, Lai S-H, et al. Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. *Cancer Res* 1986; 46: 956-961.
12. Yuan JM, Wang XL, Xiang YB, et al. Preserved foods in relation to risk of nasopharyngeal carcinoma in Shanghai, China. *Int J Cancer* 2000; 85:358-363.
13. Zur Hausen H, Schulte-Holthausen H, Klein G, et al. EBV DNA in biopsies of Burkitt tumors and anaplastic carcinomas of the nasopharynx. *Nature* 1976; 228: 1056-1058.

35. Sham JST, Cheung YK, Choy D, et al. Cranial nerve involvement and base of the skull erosion in nasopharyngeal carcinoma. *Cancer* 1991; 68:422-426.
36. Chua DTT, Sham JST, Kwong DLW, et al. Prognostic value of paranasopharyngeal extension of nasopharyngeal carcinoma. A significant factor in local control and distant metastasis. *Cancer* 1991; 78:202-210.
37. Peng J-C, Sheen T-S, Hsu M-M. Nasopharyngeal carcinoma with dermatomyositis. Analysis of 12 cases. *Arch Otolaryngol Head Neck Surg* 1995; 121:1298-1301.
38. Kavanagh BD, Halpern EC, Rosenbaum LC, et al. Syndrome of inappropriate secretion of antidiuretic hormone in a patient with carcinoma of the nasopharynx. *Cancer* 1992; 69:1315-1319.
39. Tan KCB, Nicholls J, Kung AWC, et al. Unusual endocrine presentations of nasopharyngeal carcinoma. *Cancer* 1996; 77:1967-1972.
40. van Hassett CA, John DG. Diagnosing nasopharyngeal carcinoma. *Laryngoscope* 1994; 104:103-104.
41. Cheung YK, Sham J, Cheung YL. Evaluation of skull base erosions in nasopharyngeal carcinoma: comparison of plain radiography and computed tomography. *Oncology* 1994; 51:42-46.
42. Chan MKM, Huang DP. The value of cytologic examination for nasopharyngeal carcinoma. *Ear Nose Throat J* 1990; 69:268-271.
43. Feinmesser R, Miyazaki I, Cheung R, et al. Diagnosis of nasopharyngeal carcinoma by DNA amplification of tissue obtained by fine-needle aspiration. *N Engl J Med* 1992; 326:17-21.
44. Feinmesser R, Feinmesser M, Freeman JL, et al. Detection of occult nasopharyngeal primary tumours by means of in situ hybridization. *J Laryngol Otol* 1992; 106:345-348.
45. Dictor M, Siven M, Tennvall J, et al. Determination of nonendemic nasopharyngeal carcinoma by in situ hybridization for Epstein-Barr virus EBER 1 RNA: sensitivity and specificity in cervical node metastases. *Laryngoscope* 1995; 105:407-412.
46. Chao T-Y, Chow K-C, Chang J-Y, et al. Expression of Epstein-Barr-virus -encoded RNAs as a marker for metastatic undifferentiated nasopharyngeal carcinoma. *Cancer* 1996; 78:24-29.
47. Pearson GR, Weiland LH, Neel HB III, et al. Application of Epstein-Barr virus (EBV) serology to the diagnosis of North American nasopharyngeal carcinoma. *Cancer* 1983; 51:260-268.
48. Takimoto T, Ishikawa S, Masuda K, et al. Antinuclear antibodies in the sera of patients with nasopharyngeal carcinoma. *Am J Otolaryngol* 1989; 10:399-403.
49. Neel HB III, Taylor WF. Epstein-Barr virus-related antibodies. Changes in titer after therapy for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 1990; 116:1287-1290.
50. Yong-Sheng Z, Sham JST, Ng MH, et al. Immunoglobulin A against viral capsid antigen of Epstein-Barr virus and indirect mirror examination of the nasopharynx in the detection of asymptomatic nasopharyngeal carcinoma. *Cancer* 1992; 69:3-7.
51. Chien Y-C, Chen J-Y, Liu M-Y, et al. Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. *N Engl J Med* 2001; 345:1877-1882.
52. Hao S-P, Tsang N-M, Chang K-P. Screening nasopharyngeal carcinoma by detection of the latent membrane protein 1 (LMP-1) gene with nasopharyngeal swabs. *Cancer* 2003; 97:1909-1913.
53. Teo PML, Leung SF, Yu P, et al. A comparison of Ho's, International Union Against Cancer, and American Joint Committee stage classifications for nasopharyngeal carcinoma. *Cancer* 1991; 67:434-439.
54. Beahrs OH, Henson DE, Hutter RVP, et al. American Joint Committee on Cancer. Manual for Staging of Cancer, 4th ed. Philadelphia: JB Lippincott, 1992:33-38.
55. Ho JHC. An epidemiologic and clinical study of nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1978; 4:13-187.
56. Harmer MH. TNM Classification of Malignant Tumours, 3rd ed. Geneva: International Union Against Cancer, 1978.
57. American Joint Commission Cancer Staging Manual, 6th edition. Greene FL, Page DL, Fleming ID, et al. eds. New York: Springer, 2002.
58. Shanmugaratnam K, Sobin LH, Bauer WC, et al. International Histological Classification of Tumours, No. 19, Histological Typing of Upper Respiratory Tract Tumours. Geneva: World Health Organization, 1978.
59. Shanmugaratnam K, Sobin LH, Barnes L, et al. World Health Organization International Histological Classification of Tumours. Histological Typing of Tumours of the Upper Respiratory Tract and Ear, 2nd ed. Berlin: Springer-Verlag, 1991.
60. Weiland LH. Nasopharyngeal carcinoma. In: Barnes L, ed. *Surgical Pathology of the Head and Neck*, 1st edition. New York: Marcel Dekker Inc, 1985:453-466.
61. Giffler RF, Gillespie JJ, Ayala AG, et al. Lymphoepithelioma in cervical lymph nodes of children and young adults. *Am J Surg Pathol* 1977; 1:293-302.
62. Carbone A, Mischeau C. Pitfalls in microscopic diagnosis of undifferentiated carcinoma of nasopharyngeal type (lymphoepithelioma). *Cancer* 1982; 50:1344-1351.
63. Madri JA, Barwick KW. An immunohistochemical study of nasopharyngeal neoplasms using keratin antibodies. Epithelial versus nonepithelial neoplasms. *Am J Surg Pathol* 1982; 6:143-149.
64. Sugimoto T, Hshimoto H, Enjoji M. Nasopharyngeal carcinomas and malignant lymphomas: an immunohistochemical analysis of 74 cases. *Laryngoscope* 1990; 100:742-748.
65. Carbone A, Mischeau C. Pitfalls in microscopic diagnosis of undifferentiated carcinoma of nasopharyngeal type (lymphoepithelioma). *Cancer* 1982; 50:1344-1351.
66. Khanna R, Busson P, Burrows SR, et al. Molecular characterization of antigen-processing function in nasopharyngeal carcinoma (NPC). Evidence for efficient presentation of Epstein-Barr virus cytotoxic T-cells epitopes by NPC cells. *Cancer Res* 1998; 58:310-314.
67. Shpitzer T, Kerrebijn JDF, Freeman JL, et al. Lymphoid cell infiltration into Epstein-Barr virus-positive nasopharyngeal carcinomas. *Otolaryngol Head Neck Surg* 2001; 124:188-194.
68. Looi L-M. Tumor-associated tissue eosinophilia in nasopharyngeal carcinoma. A pathologic study of 422 primary and 138 metastatic tumors. *Cancer* 1987; 59:466-470.
69. Leighton SEJ, Teo JGC, Leung SF, et al. Prevalence and prognostic significance of tumor-associated tissue eosinophilia in nasopharyngeal carcinoma. *Cancer* 1996; 77:436-440.
70. Zarate-Osorno A, Jaffe ES, Medeiros LJ. Metastatic nasopharyngeal carcinoma initially presenting as cervical lymphadenopathy. A report of two cases that resembled Hodgkin's disease. *Arch Pathol Lab Med* 1992; 116:862-865.
71. Chen CL, Su IJ, Hsu MM, et al. Granulomatous nasopharyngeal carcinoma with emphasis on difficulty in diagnosis and favorable outcome. *J Formos Med Assoc* 1991; 9:91-98.
72. Shanmugaratnam K, Chan SH, De-The G, et al. Histopathology of nasopharyngeal carcinoma. Correlations

- with epidemiology, survival rates and other biological characteristics. *Cancer* 1979; 44:1029-1044.
73. Prathap K, Looi LM, Prasad U. Localized amyloidosis in nasopharyngeal carcinoma. *Histopathology* 1984; 8:27-34.
 74. Wan S-K, Chan JKC, Lau W-H, et al. Basaloid-squamous carcinoma of the nasopharynx. An Epstein-Barr virus-associated neoplasm with morphologically identical tumors occurring in other sites. *Cancer* 1995; 76:1689-1693.
 75. Franchi A, Morani M, Massi D, et al. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. *Am J Surg Pathol* 2002; 26:1597-1604.
 76. Nomori H, Watanabe S, Nakajima T, et al. Histiocytes in nasopharyngeal carcinoma in relation to prognosis. *Cancer* 1986; 57:100-105.
 77. Gallo O, Bianchi S, Gianni A, et al. Correlation between histopathological and biological findings in nasopharyngeal carcinoma and its prognostic significance. *Laryngoscope* 1991; 101:487-493.
 78. Weiss LM, Mohaved LA, Butler AE, et al. Analysis of lymphoepithelioma and lymphoepithelioma-like carcinoma for Epstein-Barr viral genomes by in-situ hybridization. *Am J Surg Pathol* 1989; 13:625-631.
 79. Akao I, Sato Y, Mukai K, et al. Detection of Epstein-Barr virus DNA in formalin-fixed paraffin-embedded tissue of nasopharyngeal carcinoma using polymerase chain reaction and in-situ hybridization. *Laryngoscope* 1991; 101:279-283.
 80. Della Torre G, Pilotti S, Donghi R, et al. Epstein-Barr virus genomes in undifferentiated and squamous cell nasopharyngeal carcinomas in Italian patients. *Diagn Mol Pathol* 1994; 3:32-37.
 81. Tsai S-T, Jin Y-T, Su I-J. Expression of EBER1 in primary metastatic nasopharyngeal carcinoma tissues using in situ hybridization. A correlation with WHO subtypes. *Cancer* 1996; 77:231-236.
 82. Pathmanathan R, Prasad U, Sadler R, et al. Clonal proliferation of cells infected with Epstein-Barr virus in pre-invasive lesions related to nasopharyngeal carcinoma. *N Engl J Med* 1995; 333:693-698.
 83. Pak W, To KF, Lo YMD, et al. Nasopharyngeal carcinoma in-situ (NPCIS) - Pathologic and clinical perspectives. *Head Neck* 2002; 24:989-995.
 84. Choi PHK, Suen MWM, Huang DP, et al. Nasopharyngeal carcinoma: Genetic changes, Epstein-Barr virus infection or both. A clinical and molecular study of 36 patients. *Cancer* 1993; 72:2873-2878.
 85. Chen Y-J, Ko J-Y, Chen P-J. Chromosomal aberrations in nasopharyngeal carcinoma analyzed by comparative genomic hybridization. *Genes Chromosomes Cancer* 1999; 25:169-175.
 86. Costello F, Mason BR, Collins RJ, et al. A clinical and flow cytometric analysis of patients with nasopharyngeal carcinoma. *Cancer* 1990; 66:1789-1795.
 87. Cheng DS, Campbell BH, Clowry LJ, et al. DNA content in nasopharyngeal carcinoma. *Am J Otolaryngol* 1990; 11:393-397.
 88. Yip TTC, Lau WH, Cahn JKC, et al. Prognostic significance of DNA flow cytometric analysis in patients with nasopharyngeal carcinoma. *Cancer* 1998; 83:2284-2292.
 89. Masudo M, Shinokuma A, Hirakawa N, et al. Expression of bcl-2, p53 and Ki-67 and outcome of patients with primary nasopharyngeal carcinomas following DNA-damaging treatment. *Head Neck* 1998; 20:640-644.
 90. Chen Y-J, Ko J-Y, Chen P-J, et al. Chromosomal aberrations in nasopharyngeal carcinoma analyzed by comparative genomic hybridization. *Genes Chromosome Cancer* 1999; 25:169-175.
 91. Sheu L-F, Chen A, Tseng H-H, et al. Assessment of p53 expression in nasopharyngeal carcinoma. *Hum Pathol* 1995; 26:380-386.
 92. Roychowdhury DF, Tseng A Jr, Fu KK, et al. New prognostic factors in nasopharyngeal carcinoma. Tumor angiogenesis and C-erbB2 expression. *Cancer* 1996; 77:1419-1426.
 93. Shi W, Pataki I, MacMillan C, et al. Molecular pathology parameters in human nasopharyngeal carcinoma. *Cancer* 2002; 94:1997-2006.
 94. Bar-Sela, Kuten A, Ben-Eliezer S, et al. Expression of HER 2 and C-Kit in nasopharyngeal carcinoma: Implications for new therapeutic approach. *Mod Pathol* 2003; 16:1035-1040.
 95. Fan C-S, Wong N, Leung S-F, et al. Frequent c-myc and Int-2 over representations in nasopharyngeal carcinoma. *Hum Pathol* 2000; 31:169-178.
 96. Yu Y, Dong W, Li X, et al. Significance of c-Myc and Bcl-2 expression in nasopharyngeal carcinoma. *Arch Otolaryngol head Neck Surg* 2003; 129:1322-1326.
 97. Jeng Y-M, Sung M-T, Fang C-L, et al. Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma. Two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol* 2002; 26:371-376.
 98. Wang DC, Cai WM, Hu Y, et al. Long-term survival of 1035 cases of nasopharyngeal carcinoma. *Cancer* 1988; 61:2338-2341.
 99. Qin D, Hu Y, Yan J, et al. Analysis of 1379 patients with nasopharyngeal carcinoma treated by radiation. *Cancer* 1988; 61:1117-1124.
 100. Sham JST, Wei WI, Kwan WH, et al. Nasopharyngeal carcinoma. Pattern of tumor regression after radiotherapy. *Cancer* 1990; 65:216-220.
 101. Baillet JW, Mark RJ, Abemayor E, et al. Nasopharyngeal carcinoma: treatment results with primary radiation therapy. *Laryngoscope* 1992; 102: 965-972.
 102. Wei WI. Nasopharyngeal cancer: current status of management. *Arch Otolaryngol head Neck Surg* 2001; 127:766-769.
 103. Fee WE Jr, Gilmer PA, Goffinet DR. Surgical management of recurrent nasopharyngeal carcinoma after radiation failure at the primary site. *Laryngoscope* 1988; 98:1220-1226.
 104. Wei WI, Lam KH, Ho CM, et al. Efficacy of radical neck dissection for the control of cervical metastasis after radiotherapy for nasopharyngeal carcinoma. *Am J Surg* 1990; 160:439-442.
 105. Fee WE Jr, Roberson JB Jr, Goffinet DR. Long-term survival after surgical resection for recurrent nasopharyngeal cancer after radiotherapy failure. *Arch Otolaryngol Head Neck Surg* 1991; 117:1233-1236.
 106. King WWK, Teo PML, Li ARC. Pattern of failure after radical neck dissection for recurrent nasopharyngeal carcinoma. *Am J Surg* 1992; 164:599-602.
 107. Yumoto E, Gyo K, Yanagihara N. Resection of persistent nasopharyngeal carcinoma. *Skull Base Surg* 1994; 4:59-64.
 108. Decker DA, Drelichman A, Al-Sarraf M, et al. Chemotherapy for nasopharyngeal carcinoma. A ten-year comparison. *Cancer* 1983; 52:602-605.
 109. Rossi A, Malinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year randomized study. *Am J Clin Oncol* 1988; 6:1404-1410.
 110. Boussen H, Cvitkovic E, Wendling JL, et al. Chemotherapy of metastatic and/or recurrent undifferentiated

- nasopharyngeal carcinoma with cisplatin, bleomycin, and fluorouracil. *Am J Clin Oncol* 1991; 9:1675-1681.
111. Chao R, Tannock I. Chemotherapy for recurrent or metastatic carcinoma of the nasopharynx. A review of the Princess Margaret Hospital experience. *Cancer* 1991; 68:2120-2124.
 112. Chua DTT, Sham JST, Choy D, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer* 1998; 83:2270-2283.
 113. Chan ATC, Teo PML, Leung TWT, et al. The role of chemotherapy in the management of nasopharyngeal carcinoma. *Cancer* 1998; 82:1003-1012.
 114. Mahjoubi R, Bachouchi M, Munck JN, et al. Phase II trial of recombinant interferon gamma in refractory undifferentiated carcinoma of the nasopharynx. *Head Neck* 1993; 15:115-118.
 115. Lin CL, Lo WF, Lee TH, et al. Immunization with Epstein-Barr virus (EBV) peptide-pulsed dendritic cells induces functional CD8+ T-cell immunity and may lead to tumor regression in patients with EBV-positive nasopharyngeal carcinoma. *Cancer Res* 2002; 62:6952-6958.
 116. Lofgren LA, Hallgren S, Nilsson E, et al. Photodynamic therapy for recurrent nasopharyngeal cancer. *Arch Otolaryngol head Neck Surg* 1995; 121:997-1002.
 117. Kwong DLW, Nicholls J, Wei WI, et al. The time course of histologic remission after treatment of patients with nasopharyngeal carcinoma. *Cancer* 1999; 85:1446-1453.
 118. Nicholls JM, Sham J, Chan C-W, et al. Radiation therapy for nasopharyngeal carcinoma. Histologic appearances and patterns of tumor regression. *Hum Pathol* 1992; 23:742-747.
 119. Tsang N-M, Chuang C-C, Tseng C-K, et al. Presence of the latent membrane protein 1 gene in nasopharyngeal swabs from patients with mucosal recurrent nasopharyngeal carcinoma. *Cancer* 2003; 98:2385-2392.
 120. Vikram B, Mishra UB, Strong EW, et al. Patterns of failure in carcinoma of the nasopharynx: I. Failure at the primary site. *Int J Radiat Oncol Biol Phys* 1985; 11:1455-1459.
 121. Vikram B, Mishra UB, Strong EW, et al. Patterns of failure in carcinoma of the nasopharynx: Failure at distant sites. *Head Neck Surg* 1986; 8:276-279.
 122. Ahmad A, Stefani S. Distant metastases of nasopharynx carcinoma: a study of 256 male patients. *J Surg Oncol* 1986; 3:194-197.
 123. Dictor M, Silven M, Tennvall J, et al. Determination of nonendemic nasopharyngeal carcinoma by in situ hybridization for Epstein-Barr virus EBER 1 RNA: sensitivity and specificity in cervical node metastases. *Laryngoscope* 1995; 105:407-412.
 124. Baillet JW, Mark RJ, Abemayer E, et al. Nasopharyngeal carcinoma: treatment results with primary radiation therapy. *Laryngoscope* 1992; 102:965-972.
 125. Bedwinek JM, Perez LA, Keys DJ. Analysis of failure after definitive irradiation for epidermoid carcinoma of the nasopharynx. *Cancer* 1980; 45:2725-2729.
 126. Grand C, Boracchi P, Mezzanotte G, et al. Analysis of prognostic factors and proposal of a new classification for nasopharyngeal carcinoma. *Head Neck* 1990; 12:31-40.
 127. Sham JST, Cheung YK, Choy D, et al. Cranial nerve involvement and base of the skull erosion in nasopharyngeal carcinoma. *Cancer* 1991; 68:422-426.
 128. Sham JST, Wei WI, Tai PTH, et al. Multiple malignant neoplasms in patients with nasopharyngeal carcinoma. *Oncology* 1990; 47:471-474.
 129. Cooper JS, Scott C, Marchial, et al. The relationship of nasopharyngeal carcinomas and second independent malignancies based on the Radiation Therapy Oncology Group. *Cancer* 1991; 67:1673-1677.
 130. Chen C-L, Hsu M-M. Second primary epithelial malignancy of nasopharynx and nasal cavity after successful curative radiation therapy of nasopharyngeal carcinoma. *Hum Pathol* 2000; 31:227-232.

XXV. PAPILLARY ADENOCARCINOMA OF THE NASOPHARYNX

1. Robin PE, Powell DJ, Holme GM. Malignant tumours of the nasopharynx: 220 cases 1957-1966. *Clin Otolaryngol* 1980; 5:139-156.
2. Resta L, Ricco R, Santangelo A. Morphologic and classificatory considerations about 140 cases of carcinoma of the nasopharynx. *Tumori* 1983; 69:313-321.
3. Kuo T-T, Tsang N-M. Salivary gland type nasopharyngeal carcinoma. A histologic, immunohistochemical and Epstein-Barr virus study of 15 cases including a psammomatous mucoepidermoid carcinoma. *Am J Surg Pathol* 2001; 25:80-86.
4. Wenig BM, Hyams VJ, Heffner DK. Nasopharyngeal papillary adenocarcinoma. A clinicopathologic study of low-grade carcinoma. *Am J Surg Pathol* 1988; 12:946-953.
5. van Hassett CA. Papillary adenocarcinoma of the nasopharynx. *J Laryngol Otol* 1991; 105:853-854.
6. Nojog M MAM, Jalaludin M, Jayalakshmi P. Papillary adenocarcinoma of the nasopharynx—case report and review of the literature. *Med J Malaysia* 1997; 53:104-106.
7. Karkos PD, Kelleher R, Hilmi OJ, et al. Aggressive papillary tumor of the nasopharynx followed by an aggressive papillary tumour of the middle ear. A multiple site tumour? *J Laryngol Otol* 2003; 117:989-991.
8. Kennedy MT, Jordan RCK, Berean KW, et al. Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma. *J Clin Pathol* 2004; 57:932-937.
9. Cathro HP, Mills SE. Immunophenotypic differences between intestinal-type and low-grade papillary sinonasal adenocarcinoma. An immunohistochemical study of 22 cases utilizing CDX2 and MUC2. *Am J Surg Pathol* 2004; 28:1026-1032.
10. Carrizo F, Luna MA. Thyroid transcription factor-1 expression in thyroid-like nasopharyngeal papillary adenocarcinoma: report of 2 cases. *Ann Diagn Pathol* 2005; 9: 189-192.
11. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Am J Surg Pathol* 1986; 10:192-202.
12. Lopez JI, Perez A. Pharyngeal adenocarcinoma with intestinal features. *J Laryngol Otol* 1990; 104:900-902.
13. Mills SE, Garland TA, Allen MS Jr. Low-grade papillary adenocarcinoma of palatal salivary gland origin. *Am J Surg Pathol* 1984; 8:367-374.
14. Fliss DM, Zirkin H, Puterman M, et al. Low-grade papillary adenocarcinoma of buccal mucosal salivary gland origin. *Head Neck* 1989; 11:237-241.
15. Mostofi R, Wood RS, Chistison W, et al. Low-grade papillary adenocarcinoma of minor salivary glands. Case report and review of the literature. *Oral Surg Oral Med Oral Pathol* 1992; 73:591-595.
16. Wang CP, Chang YL, Chen CT, et al. Photodynamic therapy with topical 5-aminolevulinic acid as a post-operative adjunct therapy for incompletely resected primary nasopharyngeal papillary adenocarcinoma; A case report. *Lasers Surg Med* 2006; 38:435-438.

**XXVI. METASTASES TO THE NASAL CAVITY
AND PARANASAL SINUS**

1. Kent SE, Majumdar B. Metastatic tumours in the maxillary sinus. A report of two cases and a review of the literature. *J Laryngol Otol* 1985; 99:459–462.
2. Prescher A, Brors D. Metastases to the paranasal sinuses: case report and review of the literature. *Laryngorhinootologie* 2001; 80:583–594.
3. Berstein JM, Montgomery WW, Balogh K Jr. Metastatic tumors to the maxilla, nose, and paranasal sinuses. *Laryngoscope* 1966; 76:621–650.

Diseases of the External Ear, Middle Ear, and Temporal Bone

Bruce M. Wenig

*Department of Pathology and Laboratory Medicine, Beth Israel Medical Center,
St. Luke's and Roosevelt Hospitals, New York, New York, U.S.A.*

I. NORMAL DEVELOPMENT AND STRUCTURE

The ear can be considered as three distinct regions or compartments that include the external ear, the middle ear and temporal bone, and the inner ear. The external ear consists of the auricle (pinna), external auditory canal (or meatus), and the tympanic membrane at the medial end of the auditory canal. The middle ear cavity includes the ossicles, eustachian tube connecting the middle ear space to the nasopharynx, and expansion of the middle ear cavity in the form of air cells in the temporal bone. The inner ear is embedded in the petrous portion of the temporal bone and consists of a membranous (otic) labyrinth that lies within a dense bone referred to as the otic capsule that is excavated to form the osseous (periotic) labyrinth (1).

The ear is the sense organ for hearing and balance. The inner ear is the sense organ for both hearing and balance. The external and middle ears are the sound-conducting apparatus for the auditory part of the inner ear. The embryology, anatomy, and histology of the ear are complex, and beyond the scope of this chapter. A broad overview of these topics follows. For a more in-depth discussion of the embryology, anatomy, and histology of the ear as well as the role that the auditory and vestibular systems play in the physiological aspects of hearing and balance, the reader is referred to additional texts (1–9).

A. External Ear

Embryology

The external ear develops from the first branchial groove. The external auricle (pinna) forms from the fusion of the auricular hillocks or tubercles, a group of mesenchymal tissue swellings from the first and second branchial arches, which lie around the external portion of the first branchial groove (2). The external auditory canal is considered a normal remnant of the first branchial groove. The tympanic membrane forms from the first and second branchial pouches and the first branchial groove (2). The ectoderm of the first branchial groove gives rise to the epithelium on the external side, the endoderm from the first branchial

pouch gives rise to the epithelium on the internal side, and the mesoderm of the first and second branchial pouches gives rise to the connective tissue lying between the external and internal epithelia (2).

Anatomy

The outer portion of the external ear includes the auricle or pinna leading into the external auditory canal. The skeleton of the auricle consists of a single plate of elastic cartilage conforming to the shape of the ear. The lobule is the only part of the auricle that is devoid of skeletal support. The cartilage of the auricle is continuous with that of the external auditory canal. The auricle is anchored through its continuity with the cartilage of the meatus and through the skin and extrinsic muscles.

The external auditory canal or meatus extends from the concha (the part of the ear lying immediately outside the opening of the external auditory canal) to its medial limit, which is the external aspect of the tympanic membrane. The lateral portion of its wall consists of cartilage and connective tissue (1). The medial portion of its wall consists of bone. The cartilaginous part of the external auditory canal constitutes slightly less than half its total length. The bony part of the canal is formed by both the tympanic part and the petrous part of the temporal bone. In adults, the anterior and inferior walls of the cartilaginous canal are closely related to the parotid gland. The anterior wall of the bony canal is closely related to the mandibular condyle, the posterior wall to the mastoid air cells, and the medial portion of the superior wall to the epitympanic recess. The tympanic membrane (ear drum) is situated obliquely at the end of the external auditory canal sloping medially both from above downward and from behind forward.

Histology

Histologically, the auricle is essentially a cutaneous structure composed of keratinizing, stratified squamous epithelium with associated cutaneous adnexal structures that include hair follicles, sebaceous glands, and eccrine sweat glands (6). In addition to the hair

follicles and sebaceous glands, the outer third of the external auditory canal is noteworthy because of the presence of modified apocrine glands called ceruminous glands that replace the eccrine glands seen in the auricular dermis. Ceruminous glands produce cerumen and are arranged in clusters composed of cuboidal cells with eosinophilic cytoplasm often containing a granular, golden-yellow pigment. These cells have secretory droplets along their luminal border. Peripheral to the secretory cells are flattened myoepithelial cells. The ducts of the ceruminous glands terminate in the hair follicle or on the skin. The ducts of ceruminous glands lack apocrine or myoepithelial cells. In the inner portion of the external auditory canal, ceruminous glands, as well as the other adnexal structures are absent. The subcutaneous tissue is composed of fibroconnective tissue, fat, and elastic-type fibrocartilage, which give the auricle its structural support. The ear lobe is devoid of cartilage and is replaced by a pad of adipose tissue. The perichondrium is composed of loose vascular connective tissue.

Similar to the auricle, the external auditory canal is lined by keratinizing squamous epithelium that extends to include the entire canal and covers the external aspect of the tympanic membrane. The inner two-thirds of the external auditory canal contain bone rather than cartilage. Because of the absence of adnexal structures, there is relatively close apposition of the epithelium to the subjacent bone.

B. Middle Ear

Embryology

The middle ear space develops from invagination of the first branchial pouch (pharyngotympanic tube) from the primitive pharynx. The eustachian tube and tympanic cavity develop from the endoderm of the first branchial pouch; the malleus and incus develop from the mesoderm of the first branchial arch (Meckel's cartilage), while the incus develops from the mesoderm of the second branchial arch (Reichert's cartilage) (2).

Anatomy

The middle ear or tympanic cavity lies within the temporal bone between the tympanic membrane and the squamous portions of the temporal bone laterally and the petrous portion of the temporal bone surrounding the inner ear medially. The anatomical limits of the tympanic cavity include (i) lateral or internal aspect made up by the tympanic membrane and squamous portion of the temporal bone; (ii) medial aspect bordered by the petrous portion of the temporal bone; (iii) superior (roof) delimited by the tegmen tympani, a thin plate of bone that separates the middle ear space from the cranial cavity; (iv) inferior (floor) aspect bordered by a thin plate of bone separating the tympanic cavity from the superior bulb of the internal jugular vein; (v) anterior aspect delimited by a thin plate of bone separating the tympanic cavity from the carotid canal housing the

internal carotid artery; and (vi) posterior aspect delimited by the petrous portion of the temporal bone containing the mastoid antrum and mastoid air cells (1,4-6). The tympanic cavity communicates anteriorly with the nasopharynx by way of the eustachian (auditory or pharyngotympanic) tube and posteriorly with the mastoid air cells by way of the aditus and mastoid antrum.

The contents of the tympanic cavity include the ossicles (malleus, incus, and stapes), the ligaments of the ossicles, the tendons of the ossicular muscles, eustachian tube, tympanic cavity proper, epitympanic recess, mastoid cavity, and the chorda tympani of the facial (VII) nerve. The middle ear as well as the external ear function as conduits for sound conduction for the auditory part of the internal ear.

Histology

Histologically, the epithelial lining of the tympanic cavity is a single layer of respiratory epithelium of flattened to cuboidal epithelium (6). Under normal conditions, there are no glandular elements within the middle ear; the presence of glandular epithelium in the middle ear is abnormal and may represent part of a metaplastic response in the setting of chronic otitis media (COM) or can be seen in adenomatous neoplasms (6). Stratified squamous epithelium is not present in the tympanic cavity under normal conditions nor does squamous metaplasia occur in the middle ear (6). Ciliated pseudostratified columnar epithelium may be found in limited patches among the flattened or cuboidal epithelium.

The lining of the eustachian (auditory) tube is a low ciliated epithelium for much of its length, except as it approaches its nasopharyngeal end, where it becomes ciliated pseudostratified columnar epithelium containing goblet cells. In its cartilaginous portion, it also contains seromucinous glands. The eustachian tubes contain a lymphoid component, particularly in children, that is referred to as Gerlach's tubal tonsil. Reactive hyperplasia of this lymphoid component particularly in children may close off the eustachian tube, providing a desirable milieu for otitis media. The cartilage of the nasopharyngeal portion of the eustachian tube is hyaline type.

C. Inner Ear

Embryology

The first division of the ear to develop is the inner ear, which appears toward the end of the first month of gestation (2,3). The membranous labyrinth, including the utricle, saccule, three semicircular ducts, cochlear duct, and endolymphatic sac arises from the placodal thickening of the ectoderm to become a closed otic vesicle (otocyst). The membranous labyrinth, which is essentially tubular and saccular, in turn is filled with fluid, the endolymph, or endolymphatic fluid. The bony labyrinth, including the vestibule, semicircular canals, and cochlea, arises from the mesenchyme around the otic vesicle (4-6).

Anatomy

The internal (inner) ear, or labyrinth, is embedded within the petrous portion of the temporal bone and comprises the medial portion of the temporal bone adjacent to the cranial cavity. The inner ear contains the membranous labyrinth, which is surrounded by an osseous layer or bony shell termed “the osseous (bony) labyrinth.” The membranous labyrinth contains the cochlea, which is the organ of hearing, and the vestibular system, which is the system of balance (equilibrium).

Histology

The histology of the inner ear to include the osseous labyrinth and membranous labyrinth, including the organ of Corti and semicircular canals, is rather complex and beyond the scope of this chapter. The histological evaluation of the inner ear contents rarely occurs in daily practice. For further details, the readers are referred to other texts (4–6).

II. NONNEOPLASTIC LESIONS OF THE EAR AND TEMPORAL BONE

The classification of nonneoplastic lesions of the ear and temporal bone is detailed in Table 1. Many cutaneous lesions occur in and around the external ear, including (although not limited to) keloids, epidermal cysts, sebaceous cysts, and angiolymphoid hyperplasia with eosinophilia and Kimura’s disease. These entities will not be discussed in this chapter; readers are referred to the chapter on selected skin lesion for a complete discussion.

Table 1 Classification of Nonneoplastic Lesions of the Ear and Temporal Bone

External ear
Developmental (accessory tragi; first branchial cleft anomalies; others)
Infectious and inflammatory
Keloid
Epidermal and sebaceous cysts
Idiopathic cystic chondromalacia
Chondrodermatitis nodularis helicis chronicus
Angiolymphoid hyperplasia with eosinophilia/Kimura’s disease
Autoimmune systemic diseases:
Relapsing polychondritis
Gout
Wegener’s granulomatosis
Others
Exostosis
Synovial chondromatosis
Middle and inner ear, including temporal bone
Developmental and congenital anomalies
Infectious (otitis media) and inflammatory
Otic or aural polyp
Cholesteatoma
Langerhans cell histiocytosis (eosinophilic granuloma)
Heterotopias (central nervous system tissue; salivary gland)
Otosclerosis
Paget disease
Meniere disease
Others

A. Congenital Abnormalities of the Ear

The ear, including the external, middle, and internal ear, is often the target for congenital anomalies. These congenital abnormalities occur as an isolated defect or in combination with other aural and extra-aural abnormalities, and they vary from cosmetic defects to complete hearing loss. A complete discussion of the developmental defects of the ear is beyond the scope of this chapter; the interested reader is referred to other texts that discuss this subject (10–12). This section includes some of the more common developmental abnormalities that the surgical pathologist is likely to encounter in daily practice.

1. Accessory Tragi

Clinical Features

Accessory tragi, which are also referred to as accessory or supernumerary ears, accessory auricle, and polyotia, appear at birth. They may be unilateral or bilateral, sessile or pedunculated, and soft or cartilaginous skin-covered nodules or papules, which may be solitary or multiple. They are located on the skin surface often anterior to the auricle, and clinically, they may be mistaken for a papilloma (Fig. 1). Accessory tragi are thought to be related to second branchial arch anomalies. While accessory tragi may occur independent of other congenital anomalies, they may occur in association with cleft palate or lip and mandibular hypoplasia or in association with other anomalies such as Goldenhar’s syndrome (oculoauriculovertebral dysplasia) (10).

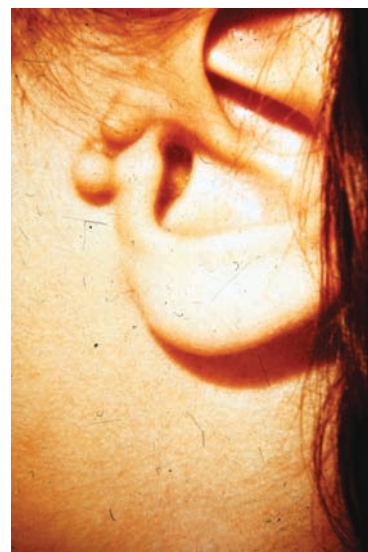


Figure 1 Accessory tragus appearing as papillomatous, skin-covered nodules located anterior to the auricle.

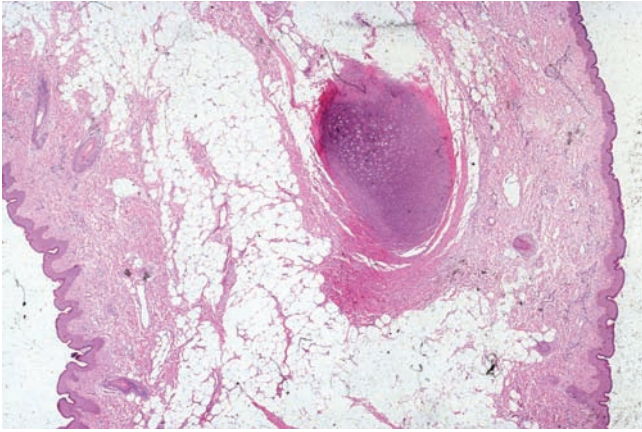


Figure 2 Histologically, accessory tragus have the appearance of the normal external auricle, as the presence of skin, including keratinizing squamous epithelium, cutaneous adnexal structures, and a central core of cartilage demonstrate.

Pathology

Microscopy. Histologically, accessory tragi recapitulate the normal external auricle and include the skin, cutaneous adnexal structures, and a central core of cartilage (Fig. 2).

Differential Diagnosis

In contrast to accessory tragus, squamous papillomas lack cutaneous adnexal structures and cartilage (13).

Treatment and Prognosis

Simple surgical excision is curative.

2. Branchial Cleft Anomalies

a. First Branchial Cleft Anomalies

Clinical Features

First branchial cleft anomalies typically occur in the area of the external ear and include cysts, sinuses, and fistulas (14). In comparison to second branchial cleft anomalies, first branchial cleft anomalies are uncommon, representing only 1% to 8% of all branchial apparatus defects. First branchial cleft anomalies may be identified in a variety of locations, including preauricular, postauricular, or infra-auricular sites, at the angle of the jaw, associated with the ear lobe, and in the external auditory canal or involving the parotid gland. Involvement of the external auditory canal may result in otalgia or otorrhea. Parotid involvement may result in an intraparotid or periparotid mass. The fistula tract in first branchial cleft anomalies may extend from the skin over or through the parotid and open in the external auditory canal.

According to Work, first branchial lesions can be divided into two types: type I and type II lesions (15,16). Type I lesions represent a first cleft anomaly only. Type I lesions are typically located medial,

inferior, or posterior to the concha and pinna. Sinuses parallel the external auditory canal and end in a blind sac at the level of the mesotympanum. The external auditory canal is intact and hearing is normal. Type II lesions typically localize to a point just below the angle of the mandible. Sinus or fistula tracts extend upward over the angle of the mandible through the parotid gland toward the external auditory canal. Rarely, cases of combined type I and type II lesions have been reported (17).

Pathology

Gross. The majority of first branchial cleft anomalies are cysts representing over two-thirds (68%) of these anomalies; (14,18) sinuses and fistulas equally make up the remainder of these lesions. The first branchial cleft cysts appear as solitary cystic lesions without an associated sinus tract.

Microscopy. Type I contains only ectodermal elements, including keratinizing squamous epithelium without adnexal structures (i.e., hair follicles, sebaceous glands, sweat glands) or cartilage, thereby duplicating the membranous external auditory canal. Type II lesions have both ectodermal and mesodermal elements, including keratinized squamous epithelium, cutaneous adnexae, and cartilage, thereby duplicating the external auditory canal and pinna. Type II anomalies are more intimately associated with the parotid gland than type I anomalies, although parotid tissue may be found in association with type I sinus or fistula tracts. Tracts associated with type II defects may terminate short of the external auditory canal or may open up in the external auditory canal near the junction of the cartilaginous portion and osseous portion of the canal; communication with the middle ear is uncommon. For either type I or type II defects, an associated prominent lymphoid component is not usually present contrasting with second branchial anomaly; only when it is inflamed or infected will there be an associated lymphoid component. Olsen and associates (14) believed that the histological features of type I and type II lesions overlapped and therefore recommended that these anomalies should be classified into cyst, sinus, or fistula.

Differential Diagnosis

The differential diagnosis includes epidermoid cysts and dermoid cysts. See chapter on diseases of the skin for a discussion of these lesions.

Treatment and Prognosis

Irrespective of the histology, complete surgical excision is the treatment of choice. Inadequate excision results in recurrence and increased risk of infection (19). Recurrence rates are increased when there are multiple preoperative infections and when there is no epithelial lining identified in the specimen (19). Incision and drainage are indicated in cases where abscesses have developed, and in this situation complete surgical excision must wait until resolution of the infection. Type II anomalies are often intimately associated with the parotid gland, necessitating a superficial parotidectomy to ensure complete excision.

Although there is no consistent relationship between the tract and the facial nerve as it courses through the parotid gland, exposure and dissection of the nerve and its branches are required in Work type II anomalies (20,21).

b. Heterotopias of the Middle Ear and Mastoid

Clinical Features

Heterotopias, which are also referred to as choristomas and ectopias, are characterized by the presence of normal-appearing tissue(s) in an anatomical location in which they are normally not found. Heterotopias that occur in the middle ear include salivary gland tissue and neuroglial tissue. Salivary gland choristomas may present with unilateral conductive hearing loss; they tend to occur more often in women and are seen over a wide age range (22–24). Salivary gland choristomas often arise in conjunction with facial nerve and ossicular chain anomalies (25). The combination of facial nerve and ossicular chain anomalies may be explained as a second branchial arch developmental abnormality. True neuronal heterotopias in which isolated neuroglial tissue is located in the middle ear and temporal bone without continuity with the central nervous system (CNS) are rare, but they have been reported (26,27). The more common occurrence in which glial type tissue is present within the middle ear/temporal bone is seen in association with an acquired encephalocele.

Pathology

Gross. Choristomas appear as lobulated, nonpulsatile soft tissue masses lying in the middle ear space with an intact tympanic membrane.

Microscopy. Histologically, the salivary tissues are composed of an admixture of seromucous glands (Fig. 3) and adipose tissue. A neuroglial heterotopia includes a heterogeneous population of cells, with

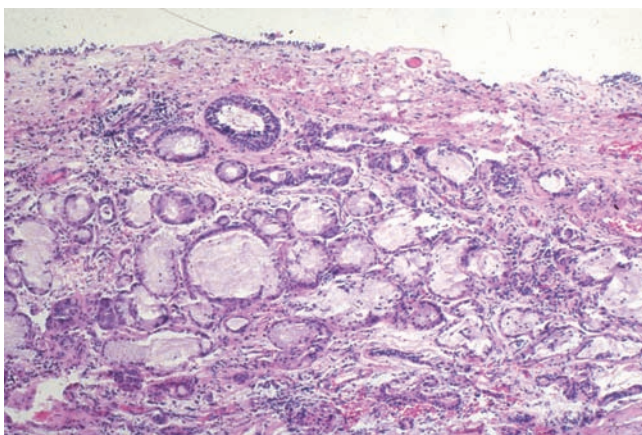


Figure 3 Middle ear heterotopia comprised of normal-appearing seromucous glands. The mass, which clinically caused conductive hearing loss, was entirely located within the middle ear space, including an intact tympanic membrane. Note the attenuated middle ear epithelium at the top of the illustration.

glial cells, histiocytes, and mature lymphocytes. Reactive alterations of the neuroglial tissue (gliosis) may be present. In addition, granulation tissue and keratinizing squamous epithelium (cholesteatoma) may be found. Immunohistochemical confirmation of neuroglial tissues includes reactivity for glial fibrillary acidic protein (GFAP).

Differential Diagnosis

In COM, a fibrillary stroma is often present, which may simulate the appearance of the neurofibrillary matrix. Reactivity for GFAP assists in confirming or excluding neuroglial tissues. The differential diagnosis also includes a glial neoplasm. Neuroglial tissues in the middle ear and mastoid generally represent an acquired encephalocele with herniation of the brain into the middle ear and mastoid via compromise of the tegmen, a thin bony shell that separates the middle ear and mastoid cavity from the temporal lobe. The tegmen may be compromised or destroyed secondary to trauma or prior surgery by a complication of otitis media or because of a congenital defect (28). Potential complications include brain abscess.

Treatment and Prognosis

Conservative surgical removal is the treatment of choice. However, choristomas often adhere to dehiscent facial nerve. If complete surgical resection will compromise the integrity of the facial nerve, then incomplete resection is justified. Biopsy for diagnostic purposes followed by observation is an alternative to surgical excision. Rarely, salivary gland ectopia may produce a neoplastic proliferation (e.g., pleomorphic adenoma) (29,30).

B. Acquired Nonneoplastic Lesions/Diseases

1. Necrotizing “Malignant” External Otitis

Clinical Features

Necrotizing malignant external otitis (NEO) is a virulent, potentially fatal form of external otitis related to *Pseudomonas aeruginosa* infection.

NEO primarily affects older patients. The typical clinical setting is that of a diabetic patient or a patient who is chronically debilitated or immunologically deficient, although NEO may occur in nondebilitated patients (31–33). NEO originates in the external auditory canal with the initial symptoms of an acute otitis externa. With the progression of disease, pain, purulent otorrhea, and swelling occur (Fig. 4). If it is left untreated, the infectious process may extend into the surrounding soft tissue structures (cellulitis), the cartilage (chondritis), the bone (osteomyelitis), the base of the skull, and the middle ear space, leading to cranial nerve palsies, meningitis, intracranial venous thrombosis, or brain abscess.

Pathogenesis and Etiology

The pathogenesis of NEO is related to tissue ischemia secondary to an underlying predisposing pathological state (diabetic angiopathy) and a migratory defect of



Figure 4 Necrotizing external otitis in a diabetic patient complaining of aural-related pain. Clinically, purulent otorrhea was present.

polymorphonuclear leukocytes related to systemic disease. These host factors that impede the inflammatory response to infection, when combined with the destructive properties of *P. aeruginosa*, are thought to be responsible for the lethal potential of NEO (31). By virtue of its endotoxins and exotoxins, neurotoxins, collagenases, and elastases, the organism is capable of causing rapid extensive tissue necrosis and necrotizing vasculitis, which compounds the destruction (31).

Pathology

Gross. The changes of NEO are most pronounced in the osseous portion of the external canal where the destructive infection usually begins. In this area, the skin becomes ulcerated, leaving a layer of thick granulation tissue covering the exposed and irregularly eroded bone, usually along the anterior and inferior surfaces of the external auditory canal (34). Necrotic tissue is abundant in fully developed NEO, and it may, along with purulent exudate, obstruct the canal.

Microscopy. The histological appearance of NEO is dominated by the presence of necrotic material and exuberant granulation tissue. The squamous epithelium is commonly ulcerated; intact epithelium may show marked reactive and/or atypical changes, including pseudoepitheliomatous hyperplasia adjacent to denuded areas.

Diffuse, heavy acute and chronic inflammation is seen in the subcutis, and a necrotizing vasculitis is commonly present. Thick, acellular collagen is seen replacing most of the tissue extending from the cartilage to the overlying dermis (Fig. 5). The bone and cartilage are necrotic, with acute and chronic inflammatory cells massively infiltrating the adjacent viable bone. Sequestra of nonviable bone or cartilage may be seen. The dermis is eventually replaced by acellular collagen. Gram-negative bacilli are easily demonstrated by tissue gram stain.

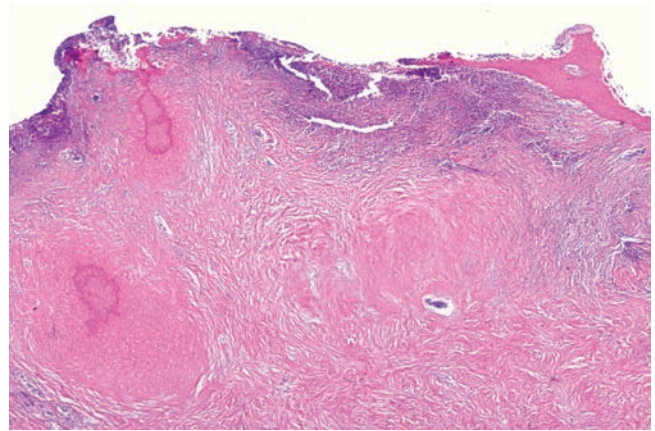


Figure 5 The histological appearance of necrotizing external otitis includes showing thick, acellular collagen replacing the skin and subcutaneous tissues with inflammation and necrosis extending within the depth of the tissue, including extension to underlying bone (osteomyelitis).

Differential Diagnosis

The infectious nature of NEO is usually evident from the clinical course and the histological findings. The presence of squamous pseudoepitheliomatous hyperplasia may suggest a squamous cell carcinoma (SCC). In general, the presence or absence of dysplastic changes and/or infiltrative growth allow for differentiating NEO from SCC. Conversely, SCC, if it is associated with extensive necrosis, may elude diagnosis by biopsy, yielding only necroinflammatory material such as one finds in NEO. Occasionally, the clinical presentation of SCC of the external auditory canal may closely mimic NEO (35,36), or the two diseases may occur concurrently (37).

Treatment and Prognosis

Antibiotics, surgical debridement, and control of diabetes mellitus in patients suffering from that disease are the treatments of choice. Hyperbaric oxygen therapy may be used as an adjunctive modality.

Mortality rates may exceed 75% if the diagnosis and treatment are delayed (38). Death may result from extensive spread of the infection to adjacent structures, including intracranial involvement. Cures can be achieved with early recognition and aggressive treatment.

2. Otitis Media

Clinical features

Otitis media is either acute or chronic infectious disease of the middle ear space. There is no gender predilection. Otitis media may occur at any age but is predominantly a childhood disease, particularly common in children younger than three years. Otoscopic examination reveals a hyperemic, opaque, bulging tympanic membrane with limited mobility; purulent

otorrhea may be present. Bilateral involvement is not uncommon. Symptoms include fever, otalgia, and decreased hearing typically preceded by several days of an upper respiratory tract infection.

Etiology

The most common organisms implicated in causing disease are *Streptococcus pneumoniae* and *Hemophilus influenza*. The middle ear infection is believed to result from infection via the eustachian tube either at the time of or following pharyngitis (bacterial or viral).

Pathology

Gross. There are no specific macroscopic features. In general, otitis media is managed medically. However, tissue is removed for histopathological examination at times. The tissue specimens usually are received as multiple small fragments of soft to rubbery granulation tissue. If tympanosclerosis is present, then the tissues may be firm to hard, consisting of calcific debris. In general, all of the tissue fragments should be processed for histological examination.

Microscopy. The histology of otitis media varies depending on the disease state (39). Acute otitis media is virtually never a surgical disease. The middle ear mucosa, which is also referred to as the mucoperiosteum, responds to infection with inflammation, hyperemia, polypoid thickening, and edema. The inflammatory infiltrate in acute otitis media is predominantly composed of polymorphonuclear leukocytes with a variable admixture of chronic inflammatory cells. Secretory otitis media refers to otitis media in which associated effusion is present behind an intact tympanic membrane. The exudate may be serous, hemorrhagic, fibrinous, mucoid, purulent, or an admixture of types (40). Acute otitis media usually heals by resorption by the mucoperiosteum. However, localized destruction of the middle ear ossicles may occur. Further, granulation tissue may develop, resulting in scar formation. Fibrosing osteitis is seen in areas of bone destruction that may result in reactive sclerotic bone.

Acute inflammatory cells may be superimposed in a case of COM. The histological changes in COM include a variable amount of chronic inflammatory cells consisting of lymphocytes, histiocytes, plasma cells, and eosinophils. Multinucleated giant cells and foamy histiocytes may be present. The middle ear low cuboidal epithelium may or may not be seen. However, glandular metaplasia (Fig. 6), a response of the middle ear epithelium to the infectious process, may be present. The glands tend to be more common in non-suppurative otitis media than in suppurative otitis media. The metaplastic glands are unevenly distributed in the tissue specimens, they are variably shaped, and they are separated by abundant stromal tissue. The glands are lined by columnar to cuboidal epithelium, with or without cilia or goblet cell metaplasia. Glandular secretions may or may not be present, so the glands may appear empty, or they may contain varying secretions, including thin (serous) or thick (mucoid) fluid content. The identification of cilia

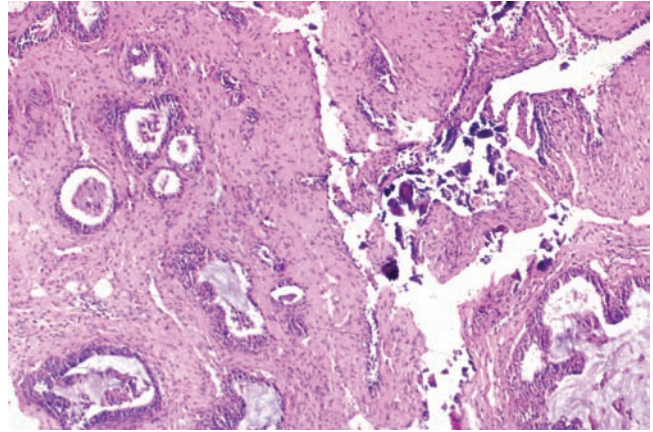


Figure 6 Chronic otitis media. The histological features of chronic otitis media include a background of chronic inflammation composed of lymphocytes with fibrosis and hemorrhage; scattered, unevenly distributed (metaplastic glands) of variable size and shape that contain thin (serous) fluid separated by abundant stromal tissue. Foci of calcification (tympanosclerosis) are present. Although not identifiable at this magnification, cilia were focally present in association with the glands, an indicator of a reactive (i.e., metaplasia) rather than neoplastic (i.e., adenoma) proliferation.

is confirmatory of middle ear glandular metaplasia because this feature is not found in association with middle ear adenomas (MEAs). Furthermore, the haphazard arrangement of the glands in the background of changes of COM should allow the observer to differentiate metaplastic from neoplastic glands.

In addition to the inflammatory cell infiltrate and glandular metaplasia, other histopathological findings that usually are seen in association with COM or that represent its sequelae include fibrosis, granulation tissue, tympanosclerosis, cholesterol granulomas, and reactive bone formation. Because of the presence of scar tissue, the middle ear ossicles may be destroyed (partially or totally), or they may become immobilized. Perforation of the tympanic membrane pars tensa may occur, with the resulting ingrowth of squamous epithelium potentially leading to the development of cholesteatoma.

3. Tympanosclerosis

Tympanosclerosis represents dystrophic mineralization (calcification or ossification) of the tympanic membrane or middle ear that is associated with recurrent episodes of otitis media (41). The incidence of tympanosclerosis in otitis media varies from 3% to 33% (42). Tympanosclerosis of the tympanic membrane can be seen in children following myringotomy and tube insertion. In this setting, the tympanosclerotic foci may or may not be permanent. Tympanosclerosis of the middle ear typically affects older patients, it represents the irreversible accumulation of mineralized material, and it is associated with conductive hearing loss (43,44).

On gross examination, tympanosclerotic foci may be localized or diffuse, and they appear as white nodules or plaques. Histologically, dense “clumps” of mineralized, calcified, or ossified material or debris can be seen within the stromal tissues or in the middle (connective tissue) aspect of the tympanic membrane (Fig. 6). Tympanosclerosis may cause scarring and ossicular fixation.

4. Cholesterol Granulomas

Cholesterol granulomas represent a foreign body granulomatous response to cholesterol crystals that are derived from the rupture of red blood cells and the resulting breakdown of the lipid layer of the erythrocyte cell membrane. Cholesterol granulomas arise in the middle ear and mastoid in any condition in which hemorrhage occurs in combination with interference in drainage and ventilation of the middle ear space; otoscopic picture is referred to as “blue ear syndrome” (45). Cholesterol granuloma of the middle ear may present as idiopathic hemotympanum; patients may also complain of hearing loss and tinnitus. The involvement of the petrous apex is more likely to be associated with sensorineural hearing loss; headaches, cranial nerve deficits, and, rarely, bone erosion with the involvement of the posterior or middle cranial fossa has been reported (46,47).

The histology of cholesterol granulomas includes the presence of irregular clear-appearing spaces surrounded by histiocytes or multinucleated giant cells (foreign body granuloma) and hemosiderosis (Fig. 7). Cholesterol granulomas are not related to cholesteatomas, but they may occur in association with them.

Differential Diagnosis

The pathological alterations are generally straightforward, but secondary changes, such as glandular metaplasia of the surface epithelium, which is the result of

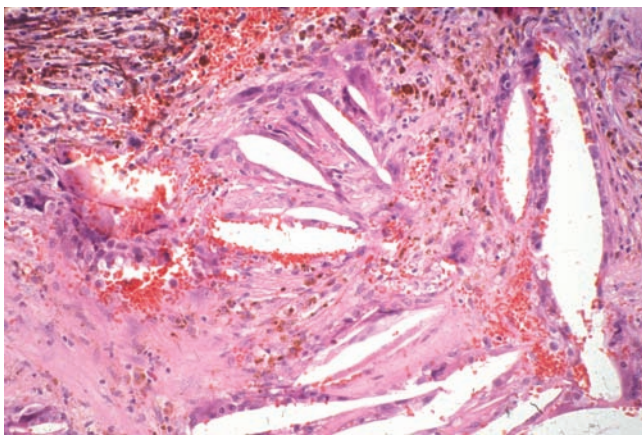


Figure 7 Cholesterol granuloma in the middle ear associated with chronic otitis media appears as empty, irregularly shaped clefts or spaces surrounded by histiocytes and multinucleated giant cells. Fresh hemorrhage and hemosiderin pigment are present.

chronic infection, may occur and might be confused with a true gland-forming neoplasm. The differential diagnosis of the glandular metaplasia seen in otitis media includes MEA. In MEAs, the histology is dominated by the presence of a diffuse glandular and/or solid cell proliferation rather than the haphazard arrangement of the glands seen in a background of changes of COM. The haphazard arrangement of the glands occurring in the background of COM and the identification of cilia confirmatory of middle ear glandular metaplasia are features that are not found in association with MEAs. Other possible lesions in the differential diagnosis of COM include cholesteatoma, Langerhan cell histiocytosis, and rhabdomyosarcoma. The absence of keratinizing squamous epithelium within the middle ear space allows for differentiation of COM from cholesteatoma. It should be noted that COM and cholesteatoma are not mutually exclusive, and in any given patient, findings diagnostic for both COM and cholesteatoma may be present. In view of the fact that the inflammatory cell infiltrate seen in cases of otitis media may be extremely dense, the pathologist must be vigilant in evaluating these specimens; this is especially true in the pediatric age group as not to overlook the presence of a rhabdomyosarcoma or Langerhans cell histiocytosis (LCH).

Treatment and Prognosis

Antibiotic therapy directed at the specific pathogen is the treatment of choice and often is curative. Recurrent infections of the middle ear are common especially in the pediatric population. In adults, an unresolving otitis media should warrant detailed examination of the nasopharynx in order to rule out the presence of a (malignant) neoplasm (e.g., nasopharyngeal carcinoma). SCCs of the middle ear are rare tumors, typically occurring in older adults suffering from long-standing history of COM. In the antibiotic era, complications associated with otitis media are not generally seen; however, if left unchecked, complications of otitis media occur, which can be divided into intratemporal complications (e.g., mastoiditis, petrositis, labyrinthitis, facial nerve paralysis) and intracranial complication (e.g., meningitis, brain abscess) (38).

5. Miscellaneous Infections

Specific causes. Uncommonly, otitis media may be caused by tuberculosis (48); syphilis (49); fungi, including *Candida*, *Mucor*, *Cryptococcus*, and *Aspergillus* (50); and actinomycosis (51). The setting for some of these infections, particularly mycoses, is often in patients who are diabetic or debilitated. In patients infected with human immunodeficiency virus (HIV) or who suffer from acquired immunodeficiency syndrome (AIDS), *Pneumocystis carinii* may be seeded by pulmonary lesions to the middle ear and temporal bone (52). In this setting, the initial clinical presentation may occur as an aural polyp that, on histological examination, shows characteristic foamy exudate containing the causative organisms. Viruses, including herpes, cytomegalovirus, rubella, rubeola, and

mumps, can infect this region, and they may result in labyrinthitis and sensorineural hearing loss (53,54).

6. Inflammatory Otic Polyp

Clinical Features

Otic (aural) polyp is an inflammatory polypoid proliferation that originates from the middle ear mucosa secondary to COM. Otic polyps may occur at any age, but they are most common in children. Symptoms include otorrhea, conductive hearing loss, and/or a mass protruding from the external auditory canal. Despite its origin from the middle ear, otic polyps may cause perforation of the tympanic membrane with extension into the external auditory canal. In this situation, the polyp may appear to be originating from the external auditory canal (55). In large polyps completely obstructing the external ear, radiographic studies are an invaluable aid in identifying the origin of the polyp. In long-standing cases, destruction (partial or complete) of the ossicles may occur.

Pathology

Gross. The gross appearance of otic polyps is that of a polypoid, soft to rubbery, tan–white–to pink–red–appearing lesion.

Microscopy. The polypoid mass is composed of a cellular infiltrate that primarily consists of a chronic inflammatory cell infiltrate, including mature lymphocytes, plasma cells, histiocytes, and eosinophils (Fig. 8) (55–57). Russell bodies or Mott cells containing large eosinophilic immunoglobulins can be seen, and they are indicative of a benign plasma cell proliferation (Fig. 8). Polymorphonuclear leukocytes may be present. The stroma includes granulation tissue varying in appearance from edematous and richly vascularized to fibrous with a decreased vascular component. Multinucleated giant cells, cholesterol granulomas, and calcific debris (tympanosclerosis) may be present. An overlying epithelium may not be seen; however, when it is present, it appears as pseudostratified columnar or cuboidal cells with or without cilia. Foci of squamous metaplasia and a glandular metaplastic proliferation may also be seen. Special stains for microorganisms are indicated to rule out an infectious etiology.

Differential Diagnosis

In general, the presence of a mixed cell population of chronic inflammatory cells indicates that the polyp is benign, so a diagnosis of a malignant hematolymphoid proliferation is not an issue. Rarely, lymphomatous or leukemic involvement of the middle ear and temporal bone occur secondary to systemic disease. The dense plasma cell component may lead to consideration of a plasmacytoma. While plasma cell dyscrasia may occur in this site in rare instances (58), the presence of mature plasma cells, Russell bodies, and polyclonality by immunohistochemistry should preclude a diagnosis of plasmacytoma. The cellular component in otic polyps may be very dense, and it may obscure an under-

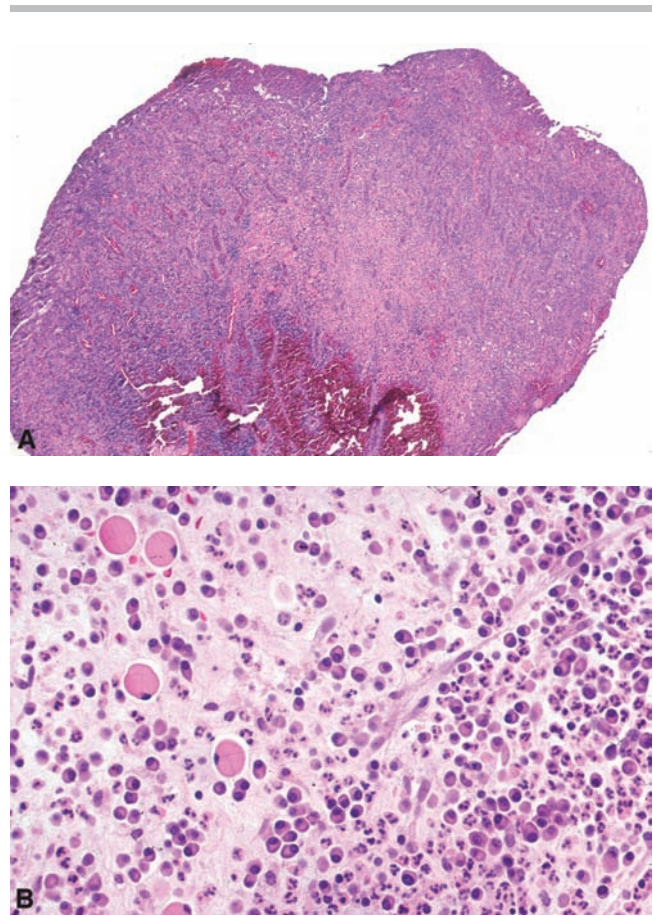


Figure 8 Otic (aural) polyp. (A) This polypoid lesion originated in the middle ear space, perforated the tympanic membrane, and protruded from the external auditory canal. Histologically, it has an exophytic or polypoid appearance with surface ulceration, a dense inflammatory cell infiltrate, and granulation tissue, including numerous blood vessels oriented perpendicular toward the surface of the lesion. (B) At higher magnification, the polyp is composed of a cellular infiltrate, primarily consisting of an admixture of mature plasma cells and polymorphonuclear leukocytes. Russell bodies, which are also referred to as Mott cells, containing large eosinophilic immunoglobulins, are seen in the left side of the illustration.

lying neoplastic process (e.g., rhabdomyosarcoma, Langerhans cell granulomatosis (LCG), carcinoma).

Treatment and Prognosis

In the absence of an infectious etiology, local surgical excision is curative.

7. Malakoplakia

Clinical Features

Malakoplakia, which is derived from Greek, means “soft plaque” and is an inflammatory disease that usually involves the genitourinary tract. Malakoplakia is an extremely uncommon lesion in the head and neck; the middle ear is one of the reported sites of occurrence

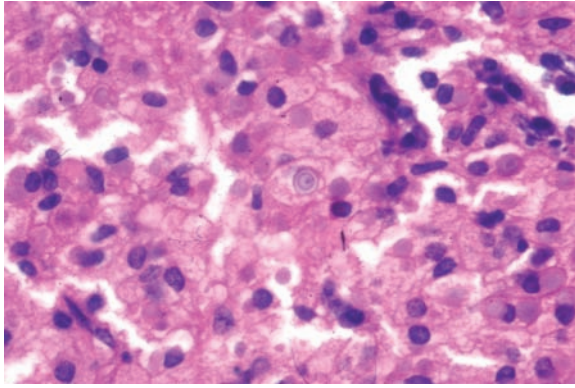


Figure 9 Malakoplakia of the middle ear is characterized by the presence of solid sheets of histiocytes with a slightly granular to vacuolated cytoplasm (Hansemann cells) and a centrally located intracytoplasmic targetoid basophilic inclusion (Michaelis-Gutmann body).

(59,60). There are no specific demographics. Symptoms relate to COM and conductive hearing loss.

Pathology

Histology. The light microscopical features include the presence of solid sheets of histiocytes with slightly granular to vacuolated cytoplasm (so-called Hansemann cells) admixed with inflammatory cells, including lymphocytes, plasma cells, and neutrophils. Intracytoplasmic diastase-resistant, periodic acid-Schiff (PAS)-positive targetoid inclusion bodies termed “Michaelis-Gutmann bodies” can be seen within occasional cells (Fig. 9). These inclusions or calcospherites can also be seen extracellularly, and they contain calcium and, frequently, iron salts, thereby showing reactivity to a von Kossa stain for calcium and a Prussian blue stain for iron. Malakoplakia is believed to represent an unusual host response to infection with a variety of organisms, and, ultrastructurally, phagolysosomes that have ingested breakdown products of bacteria, such as *Escherichia coli*, have been found.

Treatment and Prognosis

Curettage is curative.

8. Chondrodermatitis Nodularis Chronicus Helicis (Winkler Disease)

Clinical Features

Chondrodermatitis nodularis chronicus helicis (CNCH) is an idiopathic, nonneoplastic ulcerative lesion of the auricle. CNCH usually affects men in the late middle-age and older age groups, and it is considered uncommon in women (61,62). Patients present with spontaneously occurring unilateral painful nodules. Even gentle manipulation may precipitate excruciating pain, eventually prompting patients to seek treatment. CNCH most frequently occurs along the superior



Figure 10 Chondrodermatitis nodularis chronicus helicis. The lesion was painful and located along the lateral helix. Clinically, it was considered to be a carcinoma.

portion of the helix; lateral helical, antihelical, and antitragal involvement are also seen. They typically appear as round, reddish, tender areas usually measuring less than 1 cm in diameter (Fig. 10). Clinically, many cases are considered carcinomas (62).

Etiology

The etiology of CNCH is not known, but several theories have been suggested, including cold exposure, actinic damage, local trauma, and degenerative change with pressure necrosis. Because the skin of the auricle is quite thin, with little subcutaneous fat, the area may be unusually sensitive to injury. In addition, the vascular supply to the area is somewhat deficient, with the avascular cartilage depending on the dermal circulation for its sustenance. These anatomical features may predispose the auricle to the development of CNCH. Winkler (63) considered the underlying pathological event to be a cartilaginous-based process. However, the etiology appears to be linked to a primary cutaneous alteration as the cutaneous changes are more significant and they are a more constant feature. The development of CNCH is likely multifactorial, and it includes actinic damage.

Pathology

Gross. CNCH usually appears as a dome-shaped, discrete nodule with a scale crust covering a central area of ulceration that ranges in diameter from 3 to 18 mm, with an average of 7 mm. Rarely, CNCH may achieve diameters of 2 to 3 cm.

Microscopy. Histologically, the central portion of the involved epidermis is ulcerated, while the adjacent epithelium shows acanthosis, hyperkeratosis, parakeratosis, and pseudoepitheliomatous hyperplasia (Fig. 11). The base of the ulcer shows granulation tissue with a pronounced capillary proliferation, edema, fibrinoid necrosis, and an acute and/or chronic inflammatory cell infiltrate (61). The granulation tissue and inflammatory process usually involves the perichondrium and cartilage. Pain is thought to result from this

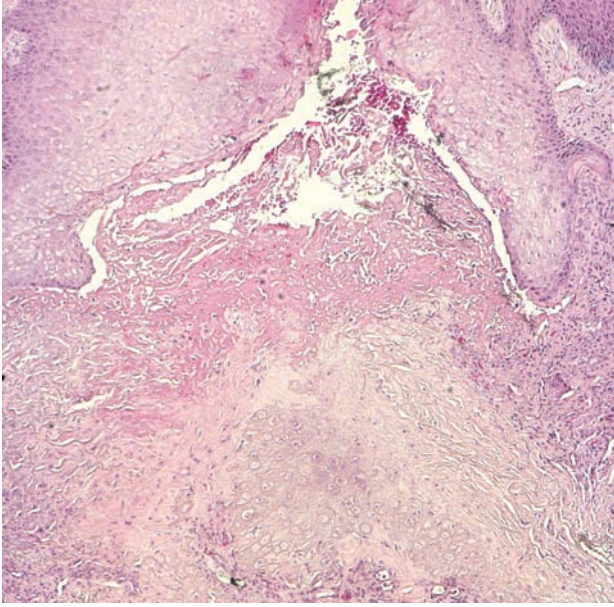


Figure 11 Chondrodermatitis nodularis chronica helices. The central portion of the involved epidermis is ulcerated, with the base of the ulcer comprised of granulation tissue that extends to the subjacent perichondrium and cartilage; perichondrial involvement is associated with pain. The surface epithelium adjacent to the ulcer shows acanthosis and hyperkeratosis

perichondrial involvement. The dermis lacks cutaneous adnexal structures in the area of the lesion, and the vasculature appears telangiectatic. Foci of fibrinoid eosinophilic material or, in some cases, frank necrobiosis of the collagen may be present. Occasionally, palisading histiocytes are seen in association with necrobiotic collagen. The changes in the auricular cartilage deep into the ulcer range from mild perichondritis through variable degrees of degenerative changes that are characterized by edema and loss of chondrocytes, with smudging (i.e., loss of basophilia) and hyalinization of the chondroid matrix. The necrotic material from the dermis and, even occasionally, fragments of degenerated cartilage may protrude into the ulcer crater. Calcification and ossification of the underlying cartilage may be present (64).

Differential Diagnosis

CNCH is frequently misdiagnosed as a cutaneous malignancy, particularly as a basal cell carcinoma (BCC) or SCC. Metzger and Goodman (61) noted a clinical diagnosis of either a malignant or premalignant lesion in 80% of the cases they reviewed. Unfortunately, the same mistake may be perpetuated by microscopical examination, particularly if the epidermal hyperplastic changes are misinterpreted as representing either SCC or a hypertrophic actinic keratosis. Careful attention to the extensive dermal changes and usually some degree of cartilaginous alterations, along with the well-demarcated nature of the epidermal proliferation and the lack of cytologic atypia in the

adjacent epidermis, should help in excluding a squamous neoplasm in cases of CNCH.

Treatment and Prognosis

Complete surgical excision, including wedge excision (65) or cartilage excision, alone (66) is the treatment of choice, and it is curative. In a minority of patients, trials with injection of glucocorticoids directly into the lesion have been effective in eradicating the lesion. Although the lesion has no malignant potential, differentiating these from BCC and SCC frequently requires biopsy.

9. Idiopathic Cystic Chondromalacia of the Auricular Cartilage (Auricular or Endochondral Pseudocyst)

Clinical Features

Idiopathic cystic chondromalacia (ICC) is a benign cystic degeneration of the auricular cartilage that is of unknown etiology. ICC typically occurs in young and middle-aged adult males, but in uncommon instances, it does occur in women (67,68). These lesions arise as unilateral, painless swellings of the cartilage without overlying ulceration or erythema over weeks to years (Fig. 12). They are occasionally bilateral (69). Although they may arise anywhere on the auricle, the scaphoid fossa is the most common site (80%) (70).

Etiology

Although trauma has been implicated in causing these lesions, no definitive connection to a prior traumatic event has been made, and the origin(s) for this condition remains unknown. Engel (71), the first to describe them in the English literature, believed that these



Figure 12 Idiopathic cystic chondromalacia appearing as (painless) swelling of the auricular cartilage with intact overlying erythematous-appearing skin.

lesions were secondary to repeated minor trauma. He attributed them to the habit of sleeping on hard pillows, although he could not substantiate his claim. Others have also believed that these lesions were traumatic in origin, citing the wearing of motor-cycle helmets, stereo headphones, the Italian birthday custom of having one's auricle pulled, and the habit of sleeping on hard pillows (67,72–75). Auricular pseudocysts may arise within the potential plane left during embryonic fusion of the auricular hillocks. Ischemic necrosis of the cartilage or the abnormal release of lysosomal enzymes by chondrocytes may also be cofactors (69,74).

Pathology

Gross. The gross appearance of ICC is that of a fluid-filled distended mass. The excised tissue may include only a fragment of the cyst wall, or, less often, it is a full-thickness excision of the ear. An intact cyst usually contains fluid that has been described as "olive oil-like" (71). The cyst wall consists of a 1- to 2-mm rim of cartilage. The cyst lining may be a smooth and glistening cartilaginous surface or may include roughened, rust-colored patches. The cyst is usually an elongated cleft, but multifocal cystic degeneration may be seen.

Microscopy. Histologically, the changes are restricted to the cartilage, within which irregular-shaped cystic areas are seen (Fig. 13). The cysts lack a cell lining, and they generally are devoid of content. An epithelial lining is absent, hence the term "pseudocyst." The cyst is the result of the loss of cartilage. The cystic cleft is often centrally placed in the cartilaginous plate. A rim of fibrous tissue along the inner rim of the cyst or a granulation tissue reaction composed of fibrovascular tissue may be observed, and scattered chronic inflammatory cells can be seen in association with the cysts. In long-standing cases, fibrous tissue may essentially obliterate the cystic space. Some examples of cystic chondromalacia are characterized by a distinctly proliferative cartilaginous response in which a thickened cartilaginous wall develops.

Differential Diagnosis

Slight cytologic atypia may be seen; however, the orderly nature of the proliferation and the associated central cystic degeneration facilitate the exclusion of malignant neoplasia (68). The differential diagnosis may also include relapsing polychondritis, subperi-chondrial hematoma, and CNCH.

Treatment and Prognosis

Complete surgical excision without distortion of the underlying cartilaginous framework is the treatment of choice, and is curative. Because of the potential for surgical-related deformity, full-thickness resection is not advocated. In addition to the obvious cosmetic concerns, long-standing lesions may result in deformity of the ear. Steroid injection alone has been unsuccessful, and it may result in cartilage deformity. Incision and drainage or curettage has shown variable success. Needle aspiration alone results in the rapid

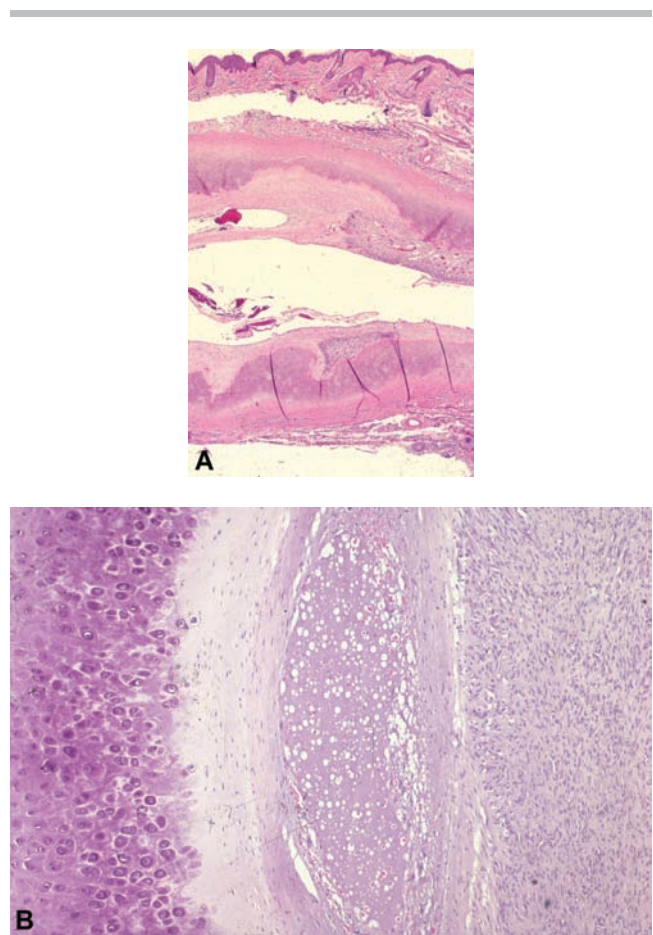


Figure 13 Idiopathic cystic chondromalacia. (A, B) Histologically, idiopathic cystic chondromalacia is characterized by the cystic degeneration of the auricular cartilage. The cysts result in the loss of cartilage. (B) The cysts, which lack a true epithelial lining (pseudocysts), are composed of fibrous tissue along the inner rim of the cyst and granulation tissue within the wall adjacent to the cartilage.

reaccumulation of fluid; however, when this is combined with bolster suture compression, long-term follow-up has shown an absence of recurrences (76).

10. Exostosis

Clinical Features

Exostoses are localized overgrowths of bone that are classically described as reactive lesions consisting of a compact proliferation of layers of bone of varied size and appearance, including nodular, mound-like, pedunculated, or flat protuberances on the surface of a bone. Broad-based lesions are referred to as exostosis, while pedunculated lesions have been termed "osteoma."

Exostoses are broad-based outgrowths of bone arising from the wall of the external auditory canal. Exostoses usually are multiple and bilateral (77). External auditory canal exostoses tend to remain asymptomatic until they reach a size sufficient to interfere with the normal egress of cerumen and

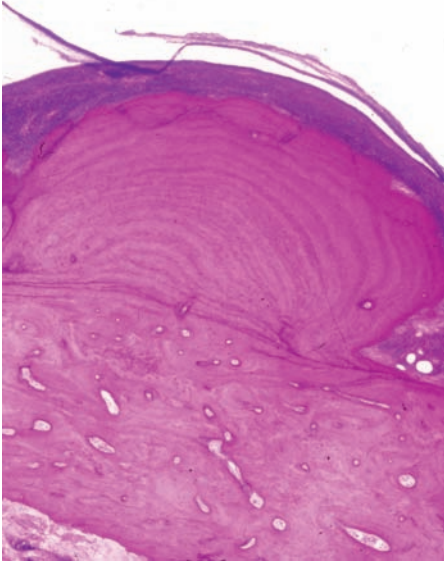


Figure 14 Exostosis of the external auditory canal appearing as a broad-based, mound-like bony proliferation lacking trabecular architecture or marrow spaces; the periosteal layers resemble the skin of an onion. A layer of periosteum with overlying thin skin covers the bone.

exfoliated skin. Most canal exostoses are asymptomatic, but external auditory canal obstruction may occur, causing recurrent episodes of external otitis, conductive hearing loss, and tinnitus (78). Exostoses of the external auditory canal affect cold water swimmers and surfers (77), with the highest incidence being found in Australia and New Zealand (79).

Pathology

Gross. The gross appearance of exostoses is usually better appreciated by the surgeon because only fragments are available to the pathologist in most cases.

Microscopy. The intact exostosis is a broad-based, mound-like bony proliferation that is similar in color and texture to the normal cortical bone (Fig. 14). A layer of periosteum with overlying thin skin covers the bone. The periosteal layers resemble the skin of an onion, and they usually lack trabecular architecture or marrow spaces.

Differential Diagnosis

The chief differential diagnosis is an osteoma, which is much less common in this location. The distinction between exostosis and osteoma usually is readily made on the basis of the clinical presentation. Some controversy exists regarding the ability to distinguish between the two lesions histologically. Some observers consider the lesions to differ histologically (77,80,81), while others do not find the microscopical features sufficiently distinctive to allow separation (82).

Treatment and Prognosis

Medical treatment resolves the symptomatic external otitis and related hearing loss. For patients who do not respond to medical treatment, transmeatal surgical excision is the treatment of choice (78).

11. Synovial Chondromatosis of the Temporomandibular Joint (TMJ)

Clinical Features

Synovial chondromatosis is a reactive process of unknown pathogenesis that is characterized by the formation of multiple cartilaginous nodules in the synovium. Many become detached and float within the joint space. Other terms for synovial chondromatosis include “synovial osteochondromatosis” and “synovial chondrometaplasia” (83).

TMJ synovial chondromatosis affects women, and it generally occurs in adults. Patients with TMJ synovial chondromatosis may present with preauricular swelling and limited motion of the joint with deviation of the mandible. TMJ synovial chondromatosis may involve the external auditory canal, resulting in an asymptomatic mass lesion (84–87).

Radiology

The radiographic features of synovial chondromatosis include the presence of numerous radiopaque loose bodies within the region of the joint, but destruction of bone is absent (88,89).

Etiology

Synovial chondromatosis is a condition in which foci of the cartilage develop in the synovial membrane of a joint, apparently through metaplasia of the sublining connective tissue of the synovial membrane. Recent studies have shown clonal chromosomal alterations in synovial chondromatosis, suggesting that this is a neoplastic lesion rather than a metaplastic and/or reactive process (90).

Pathology

Gross. The synovium may be diffusely studded with innumerable nodules. The nodules are polypoid or pedunculated with a delicate stalk, and they vary in size from as small as 1 mm to as large as 3 cm. The external surface varies from smooth to convoluted and granular.

Microscopy. Histologically, synovial chondromatosis consists of nodules of mature cartilage of varying cellularity that are found within the synovium and that lie loosely in the joint space. The cartilage may appear atypical, with hypercellularity, hyperchromasia, binucleated chondrocytes, and an increased mitotic rate (Fig. 15). Calcification and ossification may be present.

Differential Diagnosis

The presence of increased cellularity with atypical features, including binucleated chondrocytes, may suggest a diagnosis of chondrosarcoma. In such

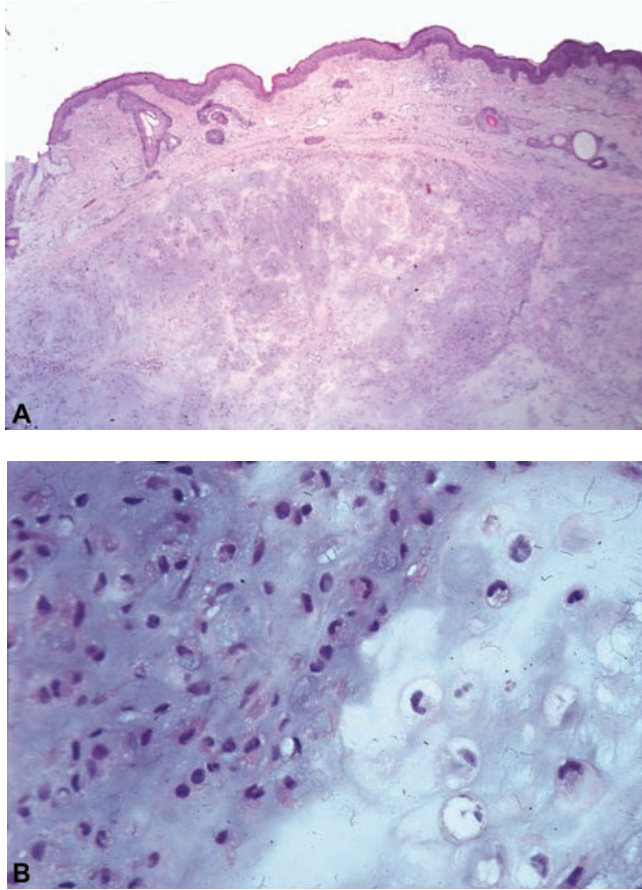


Figure 15 Synovial chondromatosis of the temporomandibular joint. (A) The lesion extended to and involved the external auditory canal histologically appearing as subcutaneous nodules of cartilage. (B) At higher magnification, the cartilage appears atypical with hypercellularity, nuclear hyperchromasia, pleomorphism, and binucleated chondrocytes but in concert with the clinical and radiographic imaging was diagnostic for a benign lesion (i.e., synovial chondromatosis) rather than a low-grade malignancy (e.g., chondrosarcoma).

examples, correlation with the radiographic appearance is essential to differentiate these lesions. The radiographic features of synovial chondromatosis include the presence of numerous radiopaque loose bodies within the region of the joint (88,89).

Treatment and Prognosis

Intraoperatively, the lesion is usually confined to the joint space, and it is easily enucleated. On occasion, the tumor may extend beyond the joint capsule into the parotid gland, the auditory canal, the temporal bone, or the cranium (91). Conservative surgical management is the treatment of choice (92). Reported cases of synovial chondrosarcoma have suggested the possibility of malignant transformation of synovial chondromatosis (93,94). Cell proliferation studies of synovial chondromatosis have shown proliferative activity that is intermediate between enchondromas and chondrosarcomas (95).

12. Acquired Cholesteatoma (Keratoma)

Cholesteatoma is a pseudoneoplastic lesion of the middle ear characterized by invasive growth and the presence of stratified squamous epithelium that forms a saclike accumulation of keratin within the middle ear space. Despite their invasive growth, cholesteatomas are not considered to be true neoplasms. The term "cholesteatoma" is a misnomer in that it is not a neoplasm nor does it contain cholesterol (96). As such, the designation of keratoma would be more accurate but the term "cholesteatoma" is entrenched in the literature. Other designations include epidermal cyst or epidermal inclusion cyst of the middle ear (97,98).

Clinical Features

Cholesteatomas occur more frequently in men than in women and are most common in the third to fourth decades of life. The middle ear space is the most common site of occurrence. Most acquired cholesteatomas arise in the pars flaccida portion of the tympanic membrane and extend into Prussak's space (98). Prussak's space is bordered laterally by the pars flaccida (Schrapnell's membrane), medially by the neck of the malleus, superiorly by the attachment of the pars flaccida to the tympanic ring near the scutum and inferiorly by the lateral or short process of the malleus (6). Initially, cholesteatomas may remain clinically silent until extensive invasion of the middle ear space and mastoid has occurred. Symptoms include hearing loss, malodorous discharge, and pain, and they may be associated with a polyp arising in the attic of the middle ear or with the perforation of the tympanic membrane. Otoscopic examination may reveal the presence of white debris within the middle ear, which is considered diagnostic.

Acquired cholesteatomas may occur in the external auditory canal (98). External ear canal cholesteatomas generally occur in older individuals, present with otorrhea and unilateral chronic pain, and does not produce a conductive hearing loss.

Radiology

Given the localization to Prussak's space, most acquired cholesteatomas displace the malleus medially and erode the adjacent bony scutum; from there, the mass may extend posteriorly via the epitympanum in the superior incudal space to the posterolateral attic and then via the aditus ad antrum to the antrum and mastoid air spaces (47). Radiographic evidence of widening of the aditus is an important diagnostic finding.

Pathogenesis

The majority of cholesteatomas are acquired and arise either de novo without a history of middle ear disease or following a middle ear infection. A small percentage of cases are congenital. The latter have also been referred to as epidermoid cysts (98,99). The pathogenesis is thought to occur via the migration of squamous epithelium from the external auditory canal or the external surface of the tympanic membrane into the

middle ear (99). The mechanism by which the epithelium may enter the middle ear probably is by a combination of events, including perforation of the tympanic membrane, particularly in its superior aspect, which is referred to as the pars flaccida or Shrapnell membrane, following an infection, coupled with the invagination or retraction of the tympanic membrane into the middle ear as a result of long-standing negative pressure on the membrane secondary to blockage or obstruction of the eustachian tube (99–101). Other theories by which cholesteatomas are thought to occur include traumatic implantation, squamous metaplasia of the middle ear epithelium, and congenital derivation.

13. Congenital Cholesteatoma

Clinical Features

Congenital cholesteatoma is a cholesteatoma of the middle ear that exists in the presence of an intact tympanic membrane presumably occurring in the absence of COM that may result in perforation or retraction of the tympanic membrane (102). Cholesteatoma of the petrous apex is an epidermoid cyst of this location, and it bears no relation to cholesteatoma of the middle ear. It likely is of congenital origin, but no cell rests have been discovered that may explain the origin of these lesions. The symptoms usually relate to the involvement of the VIIth and VIIIth cranial nerves in the cerebellopontine angle (99).

There is no gender predilection, and most congenital cholesteatomas are found in infants and young children. The majority of cases of congenital cholesteatomas are found in the antero-superior part of the middle ear (102). In early lesions, there are no symptoms, and lesions are discovered by otoscopic examination; in later lesions, the signs and symptoms may be the same as acquired cholesteatoma.

Pathogenesis

Small colonies of epidermoid cells referred to as epidermoid formations are found on the lateral anterior superior surface of the middle ear in temporal bones after 15 weeks of gestation (6,102,103). During the first postpartum year, the epidermoid colonies disappear; however, if the epidermoid cells do not disappear but continue to grow, they will become congenital cholesteatomas (102,103).

Pathology of Cholesteatoma

Gross. Cholesteatomas appear as cystic, white-to pearly appearing masses of varying size that contain creamy or waxy granular material (100).

Microscopy. The histological diagnosis is made on the basis of the presence of stratified keratinizing squamous epithelium, subepithelial fibroconnective or granulation tissue, and keratin debris (Fig. 16) (97,98). The essential diagnostic feature is the keratinizing squamous epithelium. It is important to note that the presence of keratin debris alone is not diagnostic of a cholesteatoma. The keratinizing squamous epithelium is cytologically bland, and it shows cellular maturation

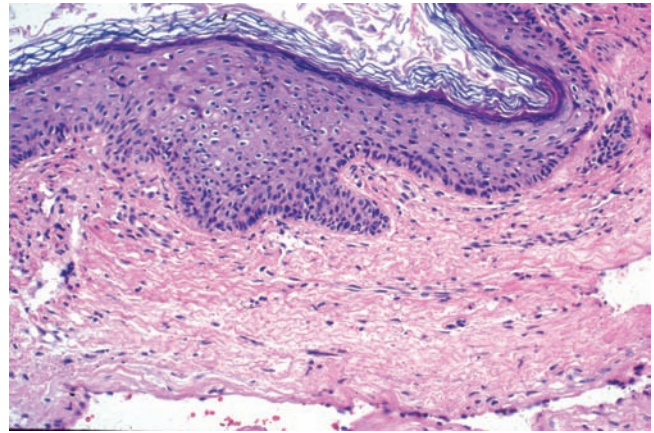


Figure 16 Cholesteatoma. The histological diagnosis of cholesteatoma is based on the finding of keratinizing squamous epithelium within the middle ear space. The keratinizing squamous epithelium shows cellular maturation and is cytologically bland, lacking dysplastic changes.

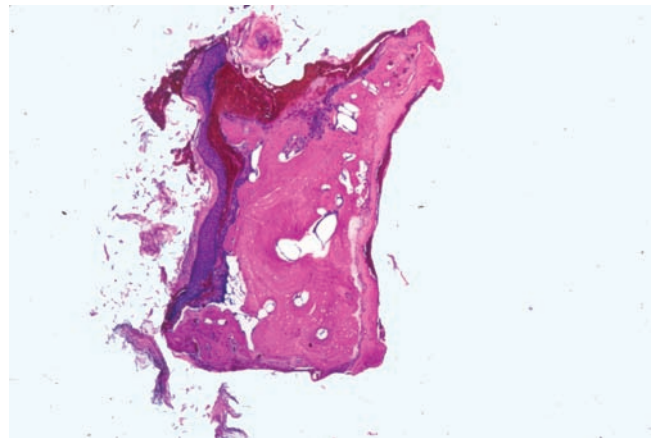


Figure 17 Cholesteatoma involving a middle ear ossicles. Although considered a nonneoplastic process and comprised of benign squamous epithelium, cholesteatomas may have infiltrative growth and destructive capability.

without evidence of dysplasia. In spite of its benign histology, cholesteatomas are “invasive,” and they have widespread destructive capabilities (Fig. 17). The destructive properties of cholesteatoma result from a combination of interrelated reasons, including mass effect with pressure erosion of the surrounding structures and the production of collagenase, which has osteodestructive capabilities (104). Collagenase is produced by both the squamous epithelial and the fibrous tissue components of the cholesteatoma.

External auditory canal cholesteatomas are composed of loosely packed, irregularly arranged keratin squames (105).

Differential Diagnosis

The differential diagnosis for external canal cholesteatoma includes keratosis obturans (KO). KO results when the normal self-cleaning mechanism of keratin maturation and lateral extrusion from the external auditory canal is defective, causing the accumulation of keratin debris deep within the bony aspect of the external auditory canal (105). The etiology of KO remains unclear. KO most commonly occurs in the first two decades of life, and the symptoms generally relate to conductive hearing loss due to the keratin plug. Pain is a common finding. The keratin debris may exert pressure effects on the bony canal wall, resulting in widening of the external auditory canal, bone remodeling, and inflamed epithelium. The histological appearance is that of tightly packed keratin squames in a lamellar pattern. The treatment for KO is debridement of the keratin plug. In contrast to KO, external ear canal cholesteatomas generally occur in individuals who are older; they present with otorrhea and unilateral chronic pain, do not produce a conductive hearing loss, and are composed of loosely packed, irregularly arranged keratin squames, histologically (105).

Cholesterol granuloma is not synonymous with cholesteatoma. These are distinctly different pathological entities that should not be confused with one another (96).

The histological diagnosis of cholesteatomas is relatively straightforward in the presence of keratinizing squamous epithelium. In contrast to cholesteatomas, SCC shows dysplastic or overtly malignant cytological features with a prominent desmoplastic stromal response to its infiltrative growth. Cholesteatomas do not transform into SCCs.

In an attempt to determine whether cholesteatomas were low-grade SCCs, Desloge and associates (106) performed DNA analysis on human cholesteatomas to determine whether ploidy abnormalities were present. In 10 cases with interpretable data, 9 were euploid, and 1 was aneuploid. These authors concluded that, because of a lack of overt genetic instability, cholesteatomas could not be considered to be malignant neoplasms. Molecular genetic evaluation has found genes induced or upregulated in cholesteatoma, including genes involved in cell proliferation and differentiation (e.g., calgranulin A, calgranulin B, psoriasin, thymosin β -10) and genes involved in cell invasion (e.g., cathepsin C, cathepsin D, cathepsin H) (107). Keratinocyte growth factor (KGF), a mesenchymal cell-derived paracrine growth factor that specifically stimulates epithelial cell proliferation is present in cholesteatomas with KGFR protein and mRNA localized in the epithelium in 72% of cases and with significant correlation between KGF+/KGFR+ expression and recurrence (108). KGF and KGFR may play a role in enhanced epithelial cell proliferative activity and recurrence of cholesteatomas (108). Angiogenesis and angiogenic growth factors have been reported to be present in cholesteatoma (109). Sudhoff and colleagues (109) reported a close relationship between the density of capillaries, degree

of inflammation, and expression of the angiogenic factors, increased number of microvessels in cholesteatomas. Further, these authors suggest that angiogenesis enables and supports the sustained migration of keratinocytes into the middle ear cavity representing a pivotal factor in the destructive behavior of middle ear cholesteatoma (109).

Treatment and Prognosis

For acquired cholesteatomas, complete surgical excision of all histological components of the cholesteatoma is the treatment of choice (100). If the cholesteatoma is not completely excised, it can have progressive and destructive growth, including widespread bone destruction, which may lead to hearing loss, facial nerve paralysis, labyrinthitis, meningitis, or brain abscess (110,111). Complete surgical resection is also the treatment of choice for congenital cholesteatomas (112). However, in comparison to acquired cholesteatomas, there typically is an absence of recurrence and complications association with congenital cholesteatomas (112,113). The most important factor in the absence of recurrence and complications is early detection, but may also relate to a different pathophysiology as compared to acquired cholesteatomas (112).

14. Langerhans Cell Histiocytosis (LCH), Langerhans Cell (Eosinophilic) Granulomatosis, and Eosinophilic Granuloma

LCH is a clonal proliferation of LCs occurring as an isolated lesion or as part of a systemic (multifocal) proliferation (114,115). The designation of LCH replaced the previous nomenclature of the group of diseases termed "histiocytosis X," which included eosinophilic granuloma, Letterer—Siwe syndrome, and Hand—Schüller—Christian disease. Lieberman and colleagues (116) suggested the designation of LC (eosinophilic) granulomatosis to indicate that the LC represents a cellular component of the dendritic cell system rather than a tissue macrophage (histiocyte).

Clinical Features

LCH most commonly occurs in the second to third decades of life, and it tends to arise in males. The lesions are most often osseous. The most frequent osseous sites involved are those in the skull, including the middle ear and the temporal bone (117–120). In patients with middle ear and temporal bone involvement, the symptoms include aural discharge, swelling of the temporal bone area, otitis media, bone pain, otalgia, loss of hearing, and vertigo (118–120). Bilateral temporal bone involvement may occur.

Radiology

Radiographic imaging on computed tomography (CT) of the skull includes (single or multiple) sharply circumscribed osteolytic lesions (120).

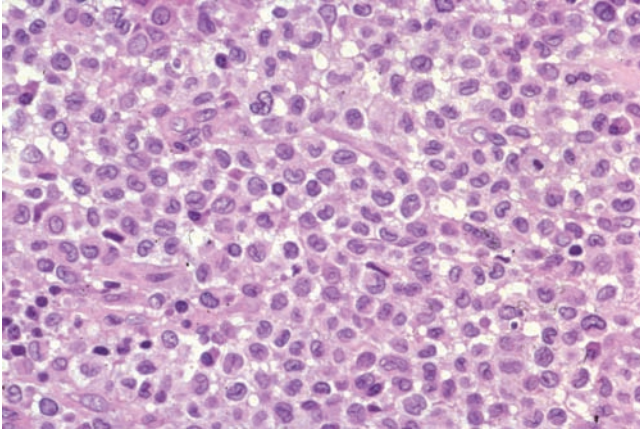


Figure 18 Langerhans cell histiocytosis. The cellular proliferation is characterized by a sheetlike proliferation of cells with lobulations and/or indentations of the nuclear membrane (reniform nuclei) representing Langerhans cells.

Pathology

Microscopy. Histologically, LCH is characterized by a proliferation of LCs, which are arranged in sheets, nests, or clusters and are composed of cells with reniform nuclei characterized by nuclear membrane lobations or indentations (Fig. 18). The nuclei have vesicular chromatin with inconspicuous to small, centrally located basophilic nucleoli and a moderate amount of eosinophilic cytoplasm. The LC may show mild pleomorphism, and mitotic figures are uncommon. An inflammatory cell infiltrate that primarily consists of eosinophils accompanies the LC. Other inflammatory cells are present, including polymorphonuclear leukocytes, plasma cells, and lymphocytes. In addition, foamy histiocytes and multinucleated giant cells may also be observed. These histiocytes may show phagocytosis of mononuclear cells.

The diagnosis of LCH is facilitated by an immunohistochemical evaluation. LCs are diffusely immunoreactive with S-100 protein (121,122) and CD1a (Fig. 19) (123). Langerin, a type II transmembrane C-type lectin associated with the formation of Birbeck granules in LC, represents a highly selective marker for LCs and the lesional cells of LCH (124). Langerin immunoreactivity (membranous and granular cytoplasmic pattern) assists in substantiating the diagnosis of LCH and in differentiating LCH from other non-LC histiocytic proliferations (124). On electron microscopy, elongated granules referred to as Langerhans or Birbeck granules can be seen within the cytoplasm of the LC (125). The foamy histiocytes and multinucleated giant cells are S-100 protein and CD1a-negative, but they do react for CD68 (KP1).

Differential Diagnosis

The histological differential diagnosis of LCH includes extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) and non-Hodgkin

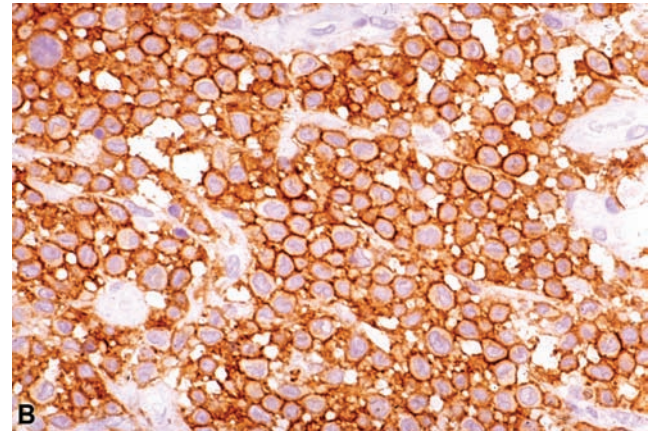
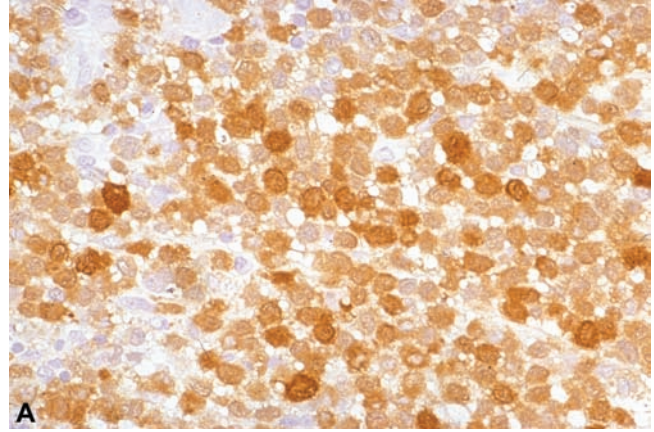


Figure 19 Langerhans cells are immunoreactive for (A) S-100 protein and (B) CD1a.

malignant lymphoma. Rosai-Dorfman disease may occasionally involve the ear and temporal bone region (126). Like LC, the cells of Rosai-Dorfman disease are S-100 protein reactive; they differ from LCs in that they are nonreactive for CD1a and Langerin (124). Differentiating LCH from a malignant lymphoproliferative disease is usually not problematic by light microscopy. If necessary, immunohistochemical stains help in differentiating LCH from a malignant lymphoma.

Treatment and Prognosis

Surgical excision (curettage) and low-dose radiation therapy (500 to 1500 rads) are the treatments of choice. The prognosis is considered very good (120). Recurrence, which may be part of a systemic or multifocal process, generally occurs within six months of the diagnosis. Failure of a new bone lesion to occur within one year of diagnosis is considered a cure. Chemotherapy is used for multifocal and/or systemic disease (120). In general, the younger the patient is at the onset of disease and the more extensive the involvement (i.e., multiple sites including bone and viscera), the worse the prognosis. Survival rates for children with multifocal disease have been reported to be 60% to 100% (120).

15. Acquired Encephalocele

Clinical Features

Acquired encephaloceles represent neuroglial tissues located within the middle ear and mastoid. Acquired encephaloceles are also referred to as ectopic or heterotopic CNS tissue, brain prolapse, or brain herniation.

There is no gender predilection. Acquired encephaloceles may occur over a wide age range but tends to occur in older individuals (127). Most often acquired encephaloceles represent an incidental finding in patients requiring surgery for COM. Associated symptoms may include unilateral conductive hearing loss, leakage of CNS tissue, and/or recurrent episodes of meningitis (127,128). In patients suspected of having ectopic neuroglial tissue in this site, radiological imaging (e.g., CT scans) may prove valuable in identifying a defect and/or connection to the CNS (128).

Pathogenesis

Generally (but not always), acquired encephaloceles represent herniation of the brain into the middle ear and mastoid via compromise of the tegmen, a thin bony shell that separates the middle ear and mastoid cavity from the temporal lobe. The connection to the CNS may not always be identified. The tegmen may be compromised or destroyed secondary to trauma, prior surgery, complication of otitis media, or congenital defect (127,128). Fracture of the temporal bone may also result in representing herniation of the brain into the middle ear and mastoid (129).

Pathology

Histology. All components of CNS tissue are present (Fig. 20); reactive alterations of the neuroglial tissue (gliosis) may be present (Fig. 20). Meninges are generally not present. The CNS tissue may be present in association with findings of other pathological processes, including COM, as well as cholesteatoma (keratinizing).

Immunohistochemical confirmation of neuroglial tissues includes reactivity with GFAP.

Differential Diagnosis

COM in which a fibrillary stroma is often present may simulate the appearance of neurofibrillary matrix. Staining for GFAP will assist in confirming or excluding neuroglial tissues.

Treatment and Prognosis

Management of the condition is surgical. For defects smaller than 1 cm in diameter, the transmastoid approach can be used (127). For defects larger than 1 cm, the combined transmastoid-minicraniotomy approach provides good access (127). Possible complications include brain abscess.

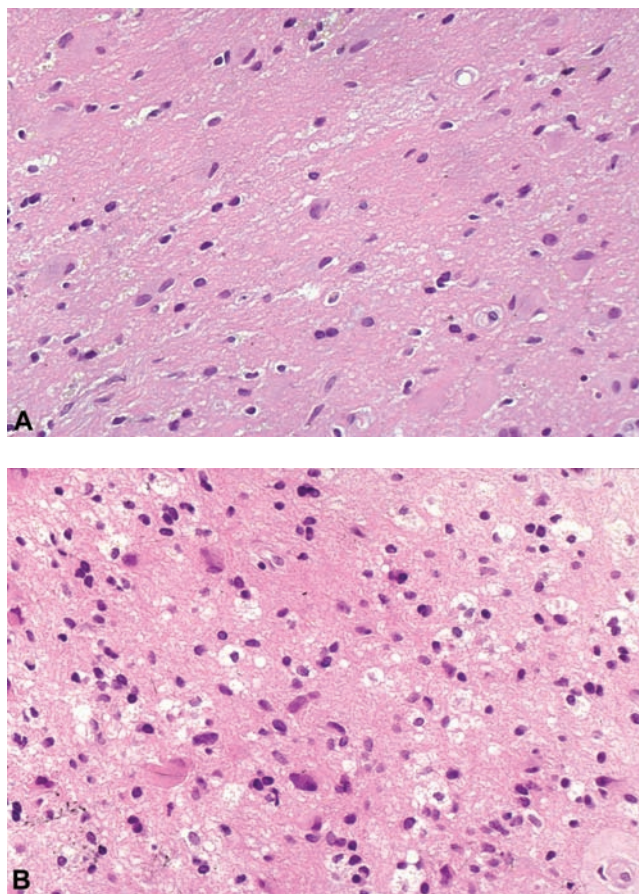


Figure 20 Acquired encephalocele in a patient with long-standing chronic otitis media who had undergone several operations. Histologically, (A) the excised tissue includes normal brain, including all cellular components of CNS tissue, and (B) reactive alterations of the neuroglial tissue (gliosis) may be identified.

16. Relapsing Polychondritis

Clinical Features

Relapsing polychondritis (RP) is an uncommon systemic episodic or relapsing disease that is characterized by the progressive degeneration of cartilaginous structures throughout the body. RP is also referred to as polychondropathy (130).

RP primarily occurs in whites, and it affects men and women equally. RP may occur at any age, but the symptoms are most frequent in the fifth to seventh decades of life. The auricular cartilage is involved, usually bilaterally, in nearly 90% of patients with RP (131–137). The affected ear is erythematous, swollen, and very tender (Fig. 21). In advanced cases, the pinna may be distorted because of destruction of the cartilage. The overlying skin is not ulcerated. The disease manifestations relapse with marked variability in both the severity and frequency of occurrence. The progression of disease may result in “cauliflower” ears and “saddle” nose deformities. The involvement of the audiovestibular system may result in hearing loss



Figure 21 Relapsing polychondritis. The affected ear is erythematous and swollen with intact (nonulcerated) overlying skin.

(conductive, sensorineural, or mixed) (133). Other cartilaginous sites, as well as noncartilaginous locations of the body, may be involved, including arthropathy (large and small joints), laryngotracheal and bronchial chondritis, nasal chondritis, cardiovascular complications (valvular insufficiency, aneurysm), ocular manifestations (episcleritis, conjunctivitis, retinopathy), and cutaneous involvement (oral and genital ulcers) (131–147).

The current clinical diagnostic criteria for RP are defined by three or more of the following: (i) recurrent chondritis of both auricles; (ii) nonerosive inflammatory arthritis; (iii) chondritis of nasal cartilages; (iv) ocular inflammation, including conjunctivitis, keratitis, scleritis and/or episcleritis, and/or uveitis; (v) chondritis of the upper respiratory tract that involves the larynx and/or tracheal cartilages; and (vi) cochlear and/or vestibular damage manifested by sensorineural hearing loss, tinnitus, and/or vertigo. The diagnosis can be confirmed when one or more of the above criteria occur in association with histological confirmation or by the presence of chondritis in two or more separate anatomical locations that respond to steroids and/or dapsone.

The laboratory findings are nonspecific, including an elevated erythrocyte sedimentation rate; mild leukocytosis; and normochromic, normocytic anemia. Antineutrophil cytoplasmic antibodies (ANCA) titers are usually negative in RP (138–140); however, elevated ANCA titers have been reported (141).

Etiology

The etiology of RP has not been clearly elucidated; however, evidence has implicated an autoimmune process. In association with RP, some patients suffer from other autoimmune disorders, including systemic

lupus erythematosus, rheumatoid arthritis, scleroderma, Sjögren syndrome, Reiter syndrome, glomerulonephritis, autoimmune thyroid disease, ulcerative colitis, pernicious anemia, and Raynaud syndrome (132,141,142).

Patients with RP have been known to have factors in their serum that react with cartilage (143). Circulating antibodies to type II collagen (144) with titers reflecting severity of disease and the documentation of immunofluorescent localization of immune complex components at the perichondral-cartilaginous interface have been reported in patients with RP (145,146). Patients with RP have immune complexes of immunoglobulins and complement detected in the biopsy specimens taken from the inflamed cartilage of the involved ear(s) (147). No evidence exists to support either a hereditary or familial predisposition.

Pathology

The histological findings in RP include perichondrial inflammation with a mixed infiltrate of lymphocytes, plasma cells, polymorphonuclear leukocytes, and occasional eosinophils that blurs the interface between the perichondrium and the auricular cartilage (Fig. 22). Loss of the usual basophilia occurs in the cartilage, which assumes an eosinophilic appearance with hematoxylin and eosin staining. At the advancing edge of the inflammation, loss of chondrocytes and destruction of the lacunar architecture are observed. As cartilage is destroyed, it is eventually replaced by fibrous tissue.

The immunomicroscopical findings include the diffuse granular deposition of immunoglobulin G (IgG) and complement protein 3 (C3) in the perichondrial fibrous tissue (148).

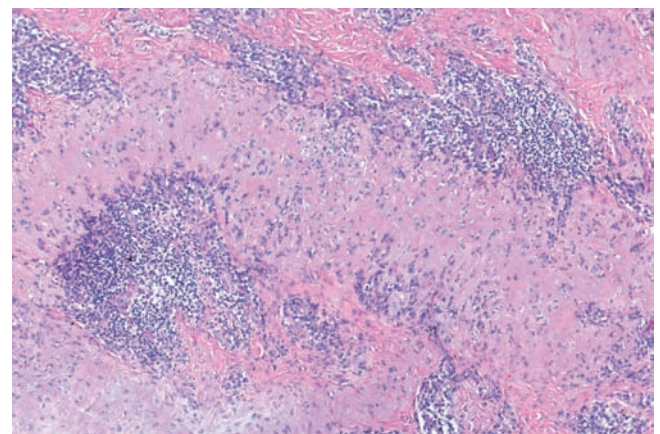


Figure 22 Relapsing polychondritis. The histological features associated with relapsing polychondritis include a mixed inflammatory cell infiltrate extending into the cartilage with blurring or obliteration of the interface between the cartilaginous plate and the adjacent fibroconnective tissues. The involved cartilage shows a loss of its normal basophilic appearance.

Differential Diagnosis

A number of diseases may be included in the clinical differential diagnosis of RP, including external otitis, acute (infectious) polychondritis, tophaceous gout, systemic vasculitides [e.g., Wegener's granulomatosis (WG)], and rheumatoid arthritis.

Treatment and Prognosis

The treatment of RP depends on the stage. In the acute stages of disease, corticosteroids are used (141). In more advanced stages, immunosuppressive agents may be used (136). The prognosis is variable and unpredictable, with some patients having a prolonged course and others suffering from a more aggressive and fulminant disease. Death may occur, and it is most often the result of respiratory tract or cardiovascular system involvement.

17. Tophaceous Gout and Pseudogout

Clinical Features

Gout is a disorder of purine metabolism or of the renal excretion of uric acid. Monosodium urate precipitates as deposits (tophi) throughout the body. One of the more common sites of gouty tophi is the helix of the ear (Fig. 23). In relationship to the ear, tophi may present as painful skin-covered firm nodules; auricular gouty tophi may be nonpainful.

The laboratory findings include the presence of elevated urinary uric acid. Additionally, leukocytosis and an increased erythrocyte sedimentation rate are often observed. The measurement of 24-hour urinary uric acid excretion helps the clinician determine whether uric acid overproduction is a cause of the hyperuricemia (149,150). In normal body tissues, sodium urate is deposited (tophi), but, in urine with a lower pH, uric acid is precipitated (149,150).



Figure 23 Gouty tophus seen on the helix of the ear. The lesion appears as a skin-covered nodule.

Etiology

Gout may occur as an inherited or acquired disease (149,150). Primary gout, which represents 90% of cases, is an inherited error of metabolism that results from either an enzymatic defect in purine synthesis or a defect in the renal excretion of uric acid. Secondary or acquired gout, which comprises the remaining 10%, occurs secondary to disorders that increase the production of uric acid (e.g., leukemias) or that decrease the excretion of uric acid (e.g., chronic renal failure).

Pathology

Microscopy. Histologically, gouty tophi are composed of needle-shaped aggregates of urate crystals with a surrounding foreign body giant cell reaction (Fig. 24). If a diagnosis of gout is suspected, the resected tissue should be fixed in absolute alcohol or any nonaqueous fixative, as the urate crystals are water soluble. Crystals demonstrate negative birefringence; when using a primary color compensator in between two polarizing lenses, the crystals will

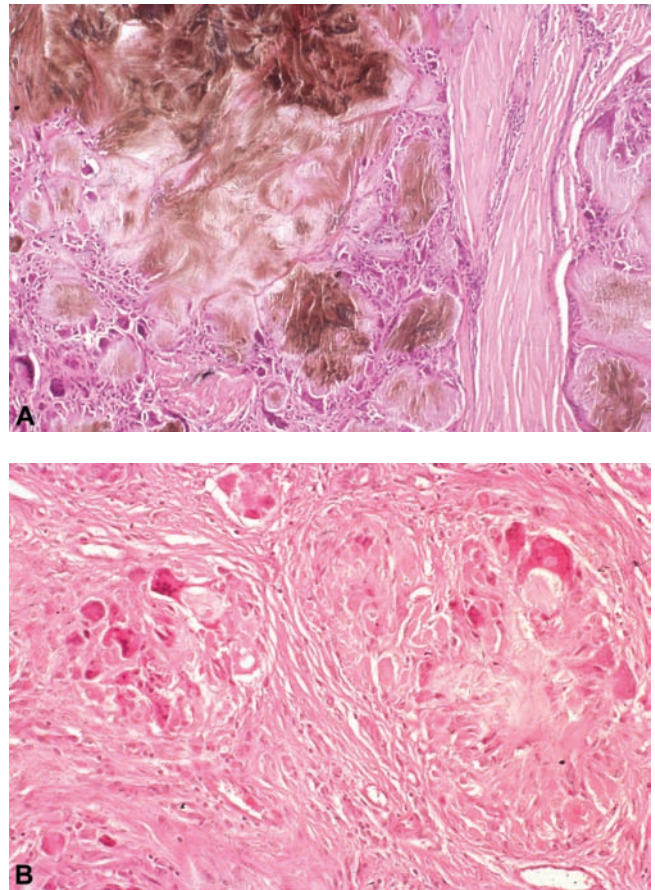


Figure 24 Histologically, (A) gout is characterized by the presence of foreign body giant cell reaction typically surrounding needle-shaped crystals, and (B) in this example, a foreign body giant cell reaction is present, but the crystals are not readily identifiable as the tissue was not fixed in absolute alcohol or a nonaqueous fixative.

change color from yellow to blue when rotating the polarizing lenses from parallel to perpendicular.

Differential Diagnosis

Tophaceous gout may share similar features with tophaceous pseudogout. The designation of pseudogout was initially coined by McCarty and associates (151) to describe the presence of calcium pyrophosphate dihydrate crystal deposition in the synovial fluid of patients with gout-like symptoms but without sodium urate crystals. Other designations include tumoral calcium pyrophosphate dihydrate (CPPD) deposition disease (152), chondrocalcinosis, and pyrophosphate arthropathy. More recently, this disease has been designated as CPPD crystal deposition disease (153). Histologically, tophaceous pseudogout is characterized by the presence of a variably cellular, chondroid-appearing tissue in which crystalline material is found (Fig. 25). The crystalline material appears rhomboid or needle shaped, and, under polarized light microscopy, the crystals show weak, positive birefringence. In decalcified material, the crystals

may be lost. A foreign body granulomatous reaction can be seen in association with the crystal deposition. Chondroid metaplasia is often present in and around the areas of CPPD deposition. Some evidence indicates that metaplastic chondrocytes may play a role in the initial precipitation of CPPD crystals. Synovial chondrometaplasia may be seen in patients with pyrophosphate arthropathy. The metaplastic chondrocytes may show cytologic atypia that could lead to a diagnosis of chondrosarcoma. This is particularly true in decalcified sections from which CPPD crystals are lost. In contrast to pseudogout, radiographic calcification in gouty tophi is relatively uncommon. In addition, the identification of the specific positive birefringence of the calcium pyrophosphate crystals that is seen in tophaceous pseudogout is not a feature of gouty tophi.

Treatment and Prognosis

The treatment is directed toward the systemic disorder.

18. Wegener's Granulomatosis

Clinical Features

WG is a systemic necrotizing vasculitis that typically involves the kidneys, lung, and upper aerodigestive tract. Otologic involvement by WG occurs in 20% to 60% of patients who have disease at these more usual sites (154–157). The most common otologic manifestations include unilateral or bilateral otitis media (serous or suppurative), perforation of the tympanic membrane, and sensorineural hearing loss (158,159). Cutaneous involvement of the external ear can include perforation of the ear lobes and external otitis (154,156–159). Facial palsy may occur as the initial manifestation of disease (155). The involvement of the middle ear may occur secondary to nasopharyngeal and sinonasal disease via the eustachian tube, or it may be due to direct involvement by disease.

Antineutrophil cytoplasmic autoantibodies (ANCA) should be elevated in the active phase of WG. Two distinct staining patterns of ANCA positivity are found, including cytoplasmic (C-ANCA) and perinuclear (P-ANCA). WG is associated with C-ANCA and infrequently with P-ANCA; (160–162) P-ANCA is more often associated with rheumatic diseases. Patients with generalized WG have a 60% to 100% C-ANCA positivity, while patients with limited WG have a 50% to 67% C-ANCA positivity (160,161). C-ANCA results can be used in establishing a diagnosis of WG in clinically suspect lesions in which the biopsies are not entirely diagnostic; false-positive results are uncommon. C-ANCA titers correlate with disease activity and recurrent disease. Proteinase-3 (PR-3) is a neutral serine proteinase present in azurophilic granules of human polymorphonuclear leukocytes and monocyte lysosomal granules. PR-3 serves as the major target antigen of ANCAs with a cytoplasmic staining pattern (c-ANCA) in WG (163,164). ANCA with specificity for PR3 are characteristic for patients with WG. Patients with WG demonstrate a significantly higher percentage of mPR3+ neutrophils than healthy controls and patients with

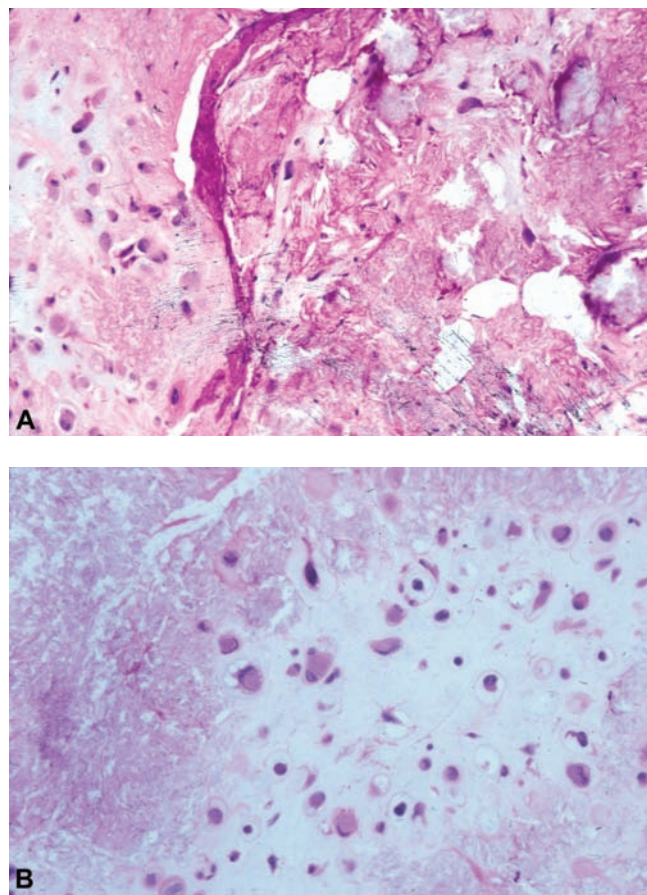


Figure 25 Tophaceous pseudogout. (A) Variably cellular chondroid-appearing tissue within which are identifiable crystalline material appearing rhomboid or needle shaped (under polarized light microscopy, the crystals showed weak positive birefringence, not shown). (B) Chondroid metaplasia is present, which may show cytological atypia.

other inflammatory diseases. The detection of ANCA directed against PR-3 (PR3-ANCA) is highly specific for WG (163,164). ANCA positivity is found only in about 50% of the patients with localized WG, whereas PR3-ANCA positivity is seen in 95% of the patients with generalized WG (164). The pathogenesis of vascular injury in WG is ascribed to ANCAs directed mainly against PR-3, and the interaction of ANCA with neutrophilic ANCA antigens is necessary for the development of ANCA-associated diseases. In patients with WG, high expression of PR-3 on the surface of nonprimed neutrophils is associated with an increased incidence and rate of relapse.

Pathology

The histological features are similar to those described in the upper aerodigestive tract (see chapter on mid-facial destructive diseases for the histological findings). Elevated serum levels of ANCA are of great assistance in those cases in which the diagnosis is suspected, but the histology may not be definitively diagnostic of WG.

Differential Diagnosis

Other autoimmune or systemic diseases that may involve the middle or inner ear include polyarteritis nodosa and rheumatoid arthritis. Polyarteritis nodosa is a necrotizing vasculitis of small and medium-sized muscular arteries. The aural-related symptoms include otitis media with effusion (165,166). Sensorineural hearing loss may be the initial presentation, or it may develop after the diagnosis has already been established (166). The histological diagnosis is dependent on the presence of necrotizing vasculitis. The treatment includes corticosteroids and immunosuppressant agents. The manifestations of rheumatoid arthritis of the audiovestibular system include conductive hearing loss due to the involvement of the incudomalleal and incudostapedial articulations (167). High-dose salicylates used in combination with steroids and nonsteroidal anti-inflammatory agents are the treatment of choice.

Treatment and Prognosis

Combined corticosteroid and immunosuppressive therapy may result in long-term remissions, and treatment is capable of reversing the hearing loss and facial palsy if the diagnosis can be established and management can be initiated early in the disease course. The prognosis for hearing is poor when appropriate treatment is not given in the early stages of the disease (157). Early diagnosis and appropriate treatment are important to prevent irreversible changes in the middle ear and inner ear.

19. Otosclerosis

Clinical Features

Otosclerosis is a disorder of the bony labyrinth and stapedial footplate that exclusively occurs in humans and is of unknown etiology. Otosclerosis means hard-

ening of the ear and is derived from Greek (ous, ear; sklerosis, hard; osis, condition), osseous ankylosis (Greek: ankoulon, to stiffen).

Otosclerosis affects women more often than men; it usually begins in the second and third decades of life and is slowly progressive. The prevalence of otosclerosis varies with race; it is more common in whites than in blacks, Asians, or Native Americans (168). Otosclerosis primarily causes conductive hearing loss that usually begins in the second and third decades of life and slowly progresses. The extent of the hearing loss directly correlates with the degree of stapedial footplate fixation. For patients with otosclerosis also to have vestibular disturbances is not uncommon (169,170). Otosclerosis usually involves both ears; however, unilateral disease can occur in up to 15% of cases (171).

Radiology

Imaging studies can confirm the clinical consideration of otosclerosis. High-resolution CT is the modality of choice for evaluating middle and inner ear structures, including labyrinthine windows, stapes foot plate, and cochlear capsule (172,173).

Etiology

Although many theories appear in the literature, the etiology of otosclerosis is unclear. Hereditary factors are often cited, although the mode of inheritance is still uncertain (174). A family history is present in a majority of cases. The majority of epidemiological studies on families with otosclerosis suggest an autosomal dominant mode of inheritance with reduced penetrance of approximately 40% (174). Genetic linkage studies have demonstrated the presence of six loci (OTSC1, OTSC2, OTSC3, OTSC4, OTSC5, and OTSC7) located on chromosomes 15q, 7q, 6p, 16q, 3q, and 6q, respectively. Although these loci have been mapped, no causative genes have been identified (174).

Pathology

Microscopy. Histologically, the initial alterations include the resorption of bone around blood vessels. Cellular fibrovascular tissue replaces the resorbed bone, resulting in the softening of the bone (otospongiosis). Immature bone is laid down with continuous active resorption and remodeling. The new bone is rich in ground substance and is deficient in collagen, but, over time, more mature bone with increased collagen and less ground substance is produced, resulting in densely sclerotic bone. This process most often begins anterior to the oval window, eventually involving the footplate of the stapes (Fig. 26). Stapedial involvement causes fixation of the stapes and the inability to transmit sound waves, resulting in conductive hearing loss. Similar pathological involvement of the inner ear may produce sensorineural hearing loss.

Differential Diagnosis

The differential diagnosis includes Paget disease (see below).

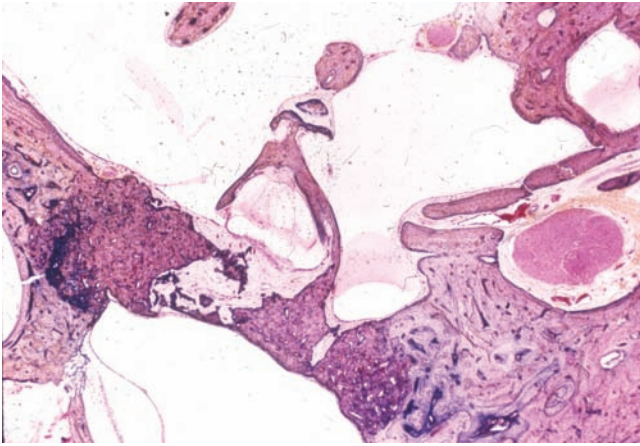


Figure 26 Otosclerosis of the stapedial footplate. This entity is characterized by densely sclerotic bone resulting in fixation of the stapes.

Treatment and Prognosis

Surgical management of the conductive hearing loss caused by stapes fixation (stapedectomy) is the treatment of choice.

20. Paget Disease of Bone

Clinical Features

Paget disease of bone, also referred to as osteitis deformans, is a chronic progressive disorder of unknown etiology. The skull and temporal bone are involved in approximately 70% of cases (175). Other sites of involvement include the external auditory canal, the tympanic membrane, the eustachian tube, the ossicles, the oval window, the round window, the internal auditory canal, the cochlea, and the endolymphatic sac (175). It is slightly more common in men than in women. Paget disease affects approximately 3% of the population older than 40 years and as high as 11% of the population older than 80 years (176). The symptoms include hearing loss, tinnitus, and vertigo. The facial nerve is spared. The hearing loss is sensorineural; mixed sensorineural and conductive; or, less often, only conductive. The hearing losses are progressive, and they are due to involvement of the osseous portion of the external auditory canal, of the ossicles, and/or of the cochlea and labyrinth.

Radiology

High-resolution CT of the temporal bone may show mixed appearance of bone thickening and sclerosis (177). In the temporal bone, the disease begins at the petrous apex and progresses inferolaterally; with progression, demineralization of the otic capsule may occur. The stapedial footplate may become involved (i.e., thickened) contributing to the (conductive) hearing loss. Frequently, the central skull is also involved.

Etiology

The etiology of Paget disease is unknown, but consideration has been given for an infectious (viral) etiology in genetically predisposed individuals.

Pathology

Paget disease is characterized by three histological phases. In the first or osteolytic phase, excessive osteoclastic activity results in bone resorption. In the second mixed or combined phase, new bone formation (osteoblastic activity) predominates over bone resorption (osteoclastic activity), with deposition of new bone next to areas of bone resorption. In the third or osteoblastic phase, increased new bone that is characterized by dense irregular masses showing a mosaic pattern of cement lines is observed.

Differential Diagnosis

The differential diagnosis includes otosclerosis. Features in Paget disease that assist in separating this from otosclerosis include a later age of onset, greater sensorineural hearing loss, enlarging calvaria, and enlargement and tortuosity of the superficial temporal artery and its anterior branches (176).

Treatment and Prognosis

Treatment is directed at slowing or preventing progression of disease by suppressing increased bone turnover using oral administration of biphosphanates, which acts by decreasing the number of osteoclasts with deposition of structurally normal bone as opposed to less disordered bone deposition. Anti-inflammatory medications are used in relieving bone and joint pain. Hearing loss is permanent and cannot be reversed by medical therapy. Sarcomatous transformation occurs in roughly 1% of cases, usually as an osteosarcoma. Osteosarcomas arising in Paget disease are highly malignant, with five-year survival rates of less than 10% (178,179).

21. Meniere Disease (Endolymphatic Hydrops, Idiopathic Endolymphatic Hydrops, or Lermoyez Syndrome)

Clinical Features

Meniere disease is an idiopathic disorder of the inner ear associated with a symptom complex of spontaneous, episodic attacks of vertigo; sensorineural hearing loss; tinnitus; and a sensation of aural fullness.

The incidence of Meniere disease varies in the literature from 157 per 100,000 people in England to 46 per 100,000 in Sweden to 7.5 per 100,000 in France (180). Meniere disease occurs slightly more frequently in women than in men (1.6:1). The peak incidence is in the fifth to seventh decades of life, but it may occur in children as well as in older individuals (9th and 10th decades). The onset of the vertigo is frequently sudden, reaching maximum intensity within a few minutes and lasting for an hour or more. It then either

subsides completely or continues as a sensation of unsteadiness for hours to days.

Etiology

The etiology is uncertain, although the incidence of Meniere disease is noted to be increased in patients with certain genetically acquired major histocompatibility complexes (MHCs), including human leukocyte antigen (HLA) B8/DR3 and Cw7, which suggest a possible autoimmune etiology (181–183). Familial occurrences of Meniere disease have been reported (184,185), although the role that genetic inheritance plays in the mode of transmission is variable.

Meniere disease appears to be due to changes in the anatomy of the membranous labyrinth as a consequence of the overaccumulation of endolymph (endolymphatic hydrops) at the expense of the perilymphatic space (185,186). Endolymph, which is produced by the stria vascularis in the cochlea and by cells in the vestibular labyrinth, circulates in a radial and longitudinal fashion. In patients with Meniere disease, the absorption of endolymph by the endolymphatic sac is believed to be inadequate (185).

Pathology

In the early stages of the disease, endolymphatic hydrops primarily involves the cochlear duct and saccule, but, in the later stages, the entire endolymphatic system is involved. Alterations of the membranous labyrinth include dilatation, outpouching, rupture, and collapse. Fistulae (unhealed ruptures) may occur. Severe cytoarchitectural and atrophic changes may occur, including the loss of neurons in the cochlea.

Treatment and Prognosis

Medical management is the mainstay of therapy. The therapy is aimed at the reduction of symptoms, and it therefore is empiric and supportive. Optimally, management should resolve the vertigo, tinnitus, and hearing loss. The current management is directed at relieving vertigo, the most debilitating of symptoms. Therapy includes prophylaxis via the reduction of endolymph accumulation by dietary modification, intermittent dehydration, diuretics; the enhancement of the microcirculation of the ear using vasodilators (e.g., betahistidine, adenosine triphosphate, isosorbide), and reduction in immunoreactivity using steroids, immunoglobulin, and allergy therapy (187). Symptomatic therapies include antivertiginous medications, antiemetics, sedatives, antidepressants, and psychiatric management. Improvements in 60% to 80% of patients have been reported (182,188). Surgical treatment is reserved for those patients who have failed medical management (approximately 10% of patients), and it includes shunting or decompression of the endolymphatic sac, labyrinthectomy, or sectioning of the vestibular nerve (187). Combined corticosteroid and immunosuppressive therapy may result in long-term remissions, and this combination is capable of reversing the hearing loss and facial palsy if the diagnosis can be established and the treatment is initiated early in the disease course.

II. NEOPLASMS OF THE EAR AND TEMPORAL BONE

The classification of neoplastic lesions of the ear and temporal bone is detailed in Table 2. Among the more common neoplasms of the external ear are those of cutaneous origin, including keratoacanthoma, squamous papilloma, seborrheic keratosis (SK), BCC, SCC, verrucous carcinoma, malignant melanoma, Merkel cell carcinoma, dermatofibrosarcoma protuberans, and others. These neoplasms will not be discussed

Table 2 Classification of Neoplasms of the Ear and Temporal Bone

I. External ear
A. Benign
Epithelial/neuroectodermal/mesenchymal
Keratoacanthoma
Ceruminal gland neoplasms
Seborrheic keratoses
Squamous papilloma
Melanocytic nevi
Dermal adnexal neoplasms
Pilomatrixoma (calcifying epithelioma of Malherbe)
Neurilemmoma/neurofibroma
Osteoma, chondroma
Hemangioma
Others
B. Malignant
Epithelial/neuroectodermal/mesenchymal
Basal cell carcinoma
Squamous cell carcinoma and variants
(verrucous carcinoma, spindle cell squamous carcinoma, adenoid squamous cell carcinoma)
Ceruminal gland adenocarcinomas
Malignant melanoma
Merkel cell carcinoma
Atypical fibroxanthoma (superficial malignant fibrous histiocytoma)
II. Middle and inner ear
A. Benign
1. Epithelial
Middle ear adenoma
Middle ear papilloma
Others
2. Neuroectodermal/mesenchymal
Jugulotympanic paraganglioma
Meningioma
Acoustic neuroma
Others
B. Indeterminant
Endolymphatic sac papillary tumor
C. Malignant
1. Epithelial
Middle ear adenocarcinoma
Primary squamous cell carcinoma
2. Mesenchymal
Rhabdomyosarcoma
Vascular (angiosarcoma; Kaposi's sarcoma)
Lymphoproliferative (malignant lymphoma, plasmacytoma)

Secondary tumors:

Squamous cell carcinoma from other head and neck sites; breast carcinoma; pulmonary adenocarcinoma; malignant melanoma; renal cell carcinoma, prostatic adenocarcinoma, others

in this chapter; readers are referred to the chapter on selected skin lesion for a complete discussion of these tumor types. However, selective cutaneous type neoplasms of the ear will be discussed in this chapter, including SCC and BCC of the pinna and external auditory canal. Rhabdomyosarcomas (RMSs) occur in the head and neck, and in children, they represent the most common aural-related malignant neoplasm. The reader is referred to the chapter on diseases of soft tissues for the discussion on RMS of the head and neck.

A. Benign Neoplasms of the External Auditory Canal

1. Ceruminal Gland Neoplasms

Ceruminal gland neoplasms are benign tumors of cerumen-secreting modified apocrine glands (ceruminal glands) located in the external auditory canal. These glands are located in the dermis of the cartilaginous (inner) portion of the external auditory canal. In general, ceruminal gland neoplasms are uncommon, but they represent one of the more common tumors of the external auditory canal. The generic designation of ceruminoma should be avoided. Ceruminal gland neoplasms should be specifically diagnosed according to the tumor type. The classification of ceruminal gland neoplasms includes benign and malignant tumors (Table 3). The benign ceruminal gland tumors include ceruminal gland adenoma (ceruminoma), pleomorphic adenoma, and syringocystadenoma papilliferum (189). The malignant ceruminal gland tumors include ceruminal gland adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma (189).

a. Ceruminal Gland Adenoma

Clinical Features

Ceruminal gland adenomas (ceruminomas) are benign neoplasms of cerumen-secreting modified apocrine glands (ceruminal glands) located in the external auditory canal. Ceruminal gland adenomas tend to affect men more than women, and they occur over a wide age range; but they are seen most frequently in the fourth to sixth decades of life. The symptoms include a slow-growing external auditory canal mass or blockage; hearing difficulty; and, infrequently, otic discharge (189–193).

Pathology

Gross. The gross appearance of ceruminal gland neoplasms includes skin-covered, circumscribed, polypoid, or rounded masses from 1 to 4 cm in diameter.

Table 3 Classification of Ceruminal Gland Neoplasms

Benign ceruminal gland tumors	
	Ceruminal gland adenoma (ceruminoma)
	Pleomorphic adenoma (benign mixed tumor)
	Syringocystadenoma papilliferum
Malignant ceruminal gland tumors	
	Ceruminal gland adenocarcinoma
	Adenoid cystic carcinoma
	Mucoepidermoid carcinoma

Ulceration is uncommon, and it may suggest a malignant neoplasm.

Microscopy. Histologically, ceruminal gland adenomas are unencapsulated but well-demarcated glandular proliferations (Fig. 27). The glands vary in size, and they may have various combinations of growth patterns, including solid, cystic, and papillary. A cribriform or back-to-back glandular pattern is commonly seen. The glands are composed of two cell layers (Fig. 27). The inner or luminal epithelial cell is cuboidal or columnar with eosinophilic cytoplasm and the decapitation-type secretion (apical “snouts”) characteristic for apocrine cells, while the outer cell layer, which is of myoepithelial differentiation, is spindled with hyperchromatic nuclei (Fig. 27). A golden yellow-brown, granular-appearing pigment can be seen in the cells of the inner lining, and this represents cerumen. Cellular pleomorphism and mitotic figures can be seen, but they are not prominent.

Diastase-resistant, PAS-positive, or mucicarmine-positive intracytoplasmic or intraluminal material may be seen. Immunohistochemical stains show the luminal cells to be strongly and diffusely immunoreactive with CK7 as well as with CD117 positivity (193). The basal cells are CK5/6, S-100 protein, and p63-positive (193). Ultrastructure evaluation includes the presence of epithelial (apocrine cell) and myoepithelial cell differentiation. Epithelial cells show features of apocrine cells, including apocrine caps, microvilli, cell junctions, secretory granules, vacuoles, lipid droplets, and siderosomes (194).

b. Ceruminal Gland Pleomorphic Adenoma

Ceruminal gland pleomorphic adenomas are uncommon tumors. The histological composition is similar to that of pleomorphic adenomas of salivary gland origin, including a variable admixture of epithelial and myoepithelial components set in a myxoid to chondromyxoid stroma.

c. Syringocystadenoma Papilliferum of Ceruminal Gland Origin

Syringocystadenoma papilliferum is a benign tumor of apocrine gland origin that usually occurs on the scalp and face area but may originate in the external auditory canal from ceruminal glands. The histology is similar to tumors of the more common cutaneous sites and to the salivary gland tumor termed “sialadenoma papilliferum” (for more details see the chapters on diseases of the salivary glands and skin).

Differential Diagnosis

The differential diagnosis for ceruminal gland adenoma includes MEA and ceruminal gland adenocarcinoma. The origin from the middle ear should allow for the identification of a MEA. However, occasionally, MEAs may perforate the tympanic membrane and appear to present as an external auditory canal mass, creating some difficulty in differentiating from a ceruminal gland adenoma. The histological features diagnostic for ceruminal gland adenoma, including (but not limited to) the presence of apocrine type secretion and intracytoplasmic cerumen should

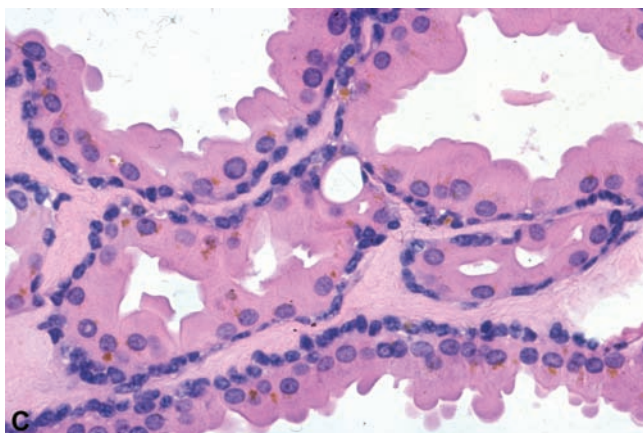
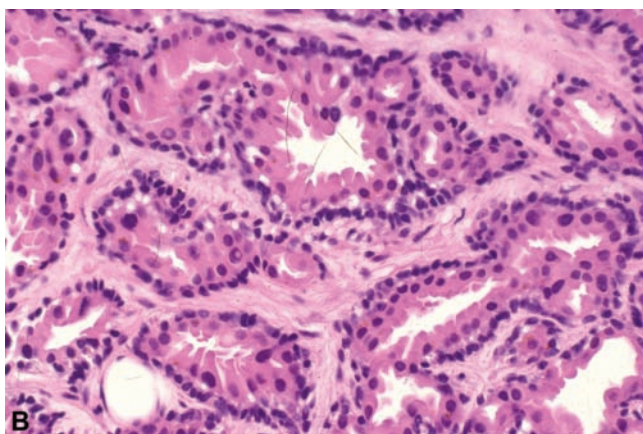
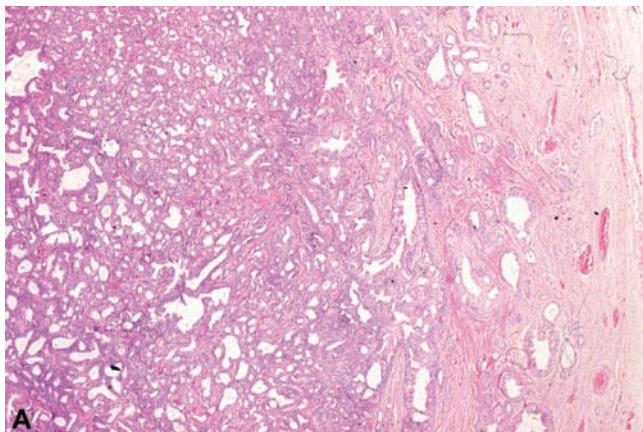


Figure 27 Ceruminal gland adenoma. (A) Ceruminal gland adenomas are unencapsulated, well-delineated glandular proliferations lacking infiltrative growth; the glands vary in size and shape and may include a back-to-back glandular pattern of growth. (B) The glands are composed of two cell layers, including inner (luminal) epithelial cells that vary in appearance from cuboidal to columnar with an eosinophilic cytoplasm and decapitation-type secretion (apical "snouts") characteristic of apocrine-derived cells and an outer layer of spindle-shaped cells, with hyperchromatic nuclei representing myoepithelial cells. (C) Intra-cytoplasmic granular, golden yellow- to brown-appearing pigment (cerumen) is seen within the inner (luminal) epithelial cells.

allow for differentiating tumor types. In contrast to ceruminal gland adenomas, ceruminal gland adenocarcinomas are cytomorphologically malignant and/or infiltrative in growth. Given the relative proximity of the parotid gland to the external auditory canal, before diagnosing a ceruminal gland pleomorphic adenoma, an origin from the parotid gland should be excluded, which requires clinical correlation.

Treatment and Prognosis

For all benign ceruminal gland neoplasms, complete surgical excision, which is curative, is the treatment of choice. Recurrences can develop, and they are related to inadequate surgical excision.

2. Benign Mesenchymal Tumors of the External Auditory Canal

Mesenchymal tumors of the external auditory canal are rare; they include osteoma (195), chondroma (196), leiomyoma (197), Schwannoma (198), and myxomas (199). In contrast to exostosis, osteomas are true neoplasms of bone that are capable of unlimited growth. Osteomas occur in the external auditory canal and present as an asymptomatic solitary mass. Histologically, osteomas are composed of mature bone with associated intraosseous fibrovascular tissue. Surgical excision is curative.

Myxomas of the external ear and external auditory canal have been described in an autosomal dominant syndrome complex that includes myxomas in other locations, most notably cardiac sites; spotty pigmentation; endocrine tumors; and schwannomas (199). Myxomas are characterized by the presence of sparse cellularity and a paucity of blood vessels (Fig. 28). The lesion consists chiefly of mucoid material in which a loose framework of reticulin fibers is suspended. The cellular component consists of a population of spindled-to-stellate cells with tiny pyknotic

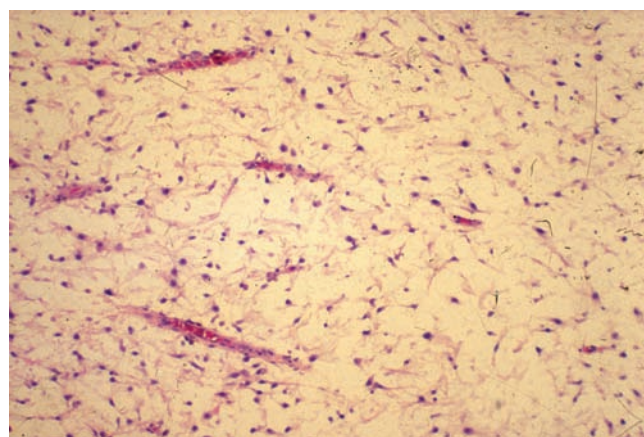


Figure 28 Myxoma of the external auditory canal is histologically characterized by sparsely cellular lesion that consists of a bland-appearing spindled to stellate cells with associated myxoid stroma.

nuclei and delicate cytoplasmic process. Cellular pleomorphism is not seen. A pseudocapsule of condensed reticulin fibers and compressed host tissue, particularly skeletal muscle, surrounds the periphery of the tumor. The myxoid matrix in myxoma stains with Alcian blue, and it is hyaluronidase sensitive. Mucicarmine and colloidal iron also stain the material. The cellular component of myxomas is vimentin-positive, but it does not express skeletal muscle antigens or S-100 protein. Although soft tissue myxomas lack a discrete capsule, they rarely recur after excision.

Myxoid change occurs in a variety of benign neoplasms, including neurofibroma, neurilemmoma, and lipoma, and it may mimic myxoma, especially in limited biopsy material. Of greater concern is the histological pattern in myxomas, which may mimic myxoid soft tissue malignancies. These, particularly embryonal rhabdomyosarcomas, as well as myxoid malignant fibrous histiocytoma (MFH), myxoid liposarcoma, and myxoid chondrosarcoma, are much more common in this location. In contrast to myxoma, sarcomas display much greater cellularity and a richer vascular pattern. Furthermore, the cytological features differ. Cellular pleomorphism and increased numbers of mitotic figures are seen in sarcomas. Differentiated cell types, such as multinucleated giant cells in myxoid MFH, lipoblasts in liposarcoma, rhabdomyoblasts in rhabdomyosarcoma, and atypical chondroblasts in chondrosarcoma, are distinctive features.

For myxomas, surgery is the treatment of choice. Although soft tissue myxomas lack a discrete capsule, they rarely recur after excision.

B. Benign Neoplasms of the Middle Ear and Temporal Bone

1. Middle Ear Adenoma

Clinical Features

MEA is a benign glandular neoplasm originating from the middle ear mucosa (200,201). MEA occurs equally in both genders and over a wide age range, but it is most common in the third to fifth decades of life. Any portion of the middle ear may be affected, including the eustachian tube, mastoid air spaces, ossicles, and chorda tympani nerve. The most common symptom is unilateral conductive hearing loss, but fullness, tinnitus, and dizziness may also occur. Pain, otic discharge, and facial nerve paralysis rarely occur, and, if they are present, they may be indicative of a malignant process. In the majority of cases, otoscopic examination identifies an intact tympanic membrane with a tumor that is confined to the middle ear space with possible extension to the mastoid. Occasionally, the adenoma perforates through the tympanic membrane with extension into and presentation as an external auditory canal mass.

Radiology

In its more typical radiological presentation, MEA appears as a relatively avascular soft tissue density without evidence of destructive, invasive, or erosive properties (201).

Etiology

There are no known etiological factors related to the development of MEA. MEAs are not associated with a history of COM. Concurrent cholesteatomas may be seen with MEA, but no known association exists between these two lesions.

Pathology

Gross. MEAs are gray-white to red-brown, rubbery to firm masses free of significant bleeding on manipulation.

Microscopy. Histologically, MEAs are unencapsulated lesions with gland or tubule formation as well as solid, sheetlike, trabecular, cystic, and cribriform growth patterns (Fig. 29). The neoplastic glands occur individually or have back-to-back growth. The glands are composed of a single layer of cuboidal to columnar cells with a varying amount of eosinophilic cytoplasm and a round to oval hyperchromatic nucleus. Nucleoli may be seen, and, generally, they are eccentrically located. The cells may have a prominent plasmacytoid appearance that is particularly evident in the more solid areas of growth but also in the cells forming the glandular

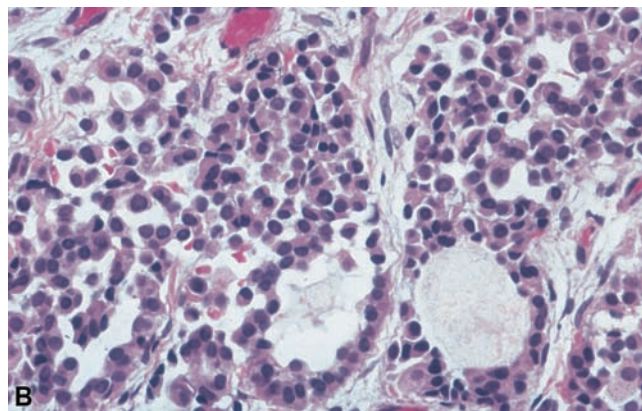
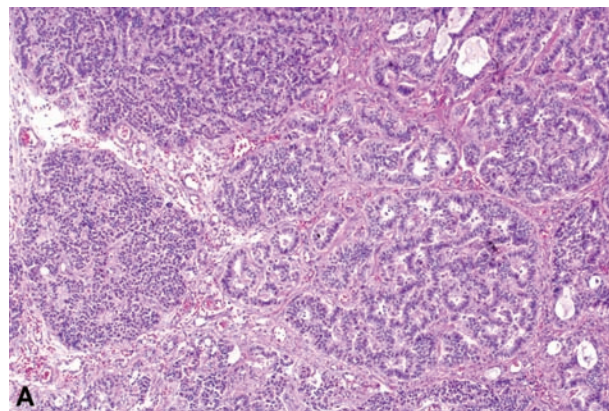


Figure 29 (A) Middle ear adenoma composed of a diffuse gland-forming proliferation. The glands may appear individually, or they may have back-to-back growth. (B) The neoplastic cells have a prominent plasmacytoid appearance evident in the solid areas as well as in association with the glands.

Table 4 Immunohistochemical Reactivity of selected Middle Ear and Temporal Bone Neoplasms

	CK	EMA	CG	SYN	S100	NSE	GFAP	VIM	DES	Myf4
MEA	+	+	—	—	—	—	—	—	—	—
MEA-NE	+	+	+	+	V	+	—	—	—	—
JTP	—	—	+	+	+ ^a	+	—	—	—	—
MEN	—	+	—	—	—	—	—	+	—	—
AN	—	—	—	—	+	+	—	—	—	—
ESPT	v	v	—	—	v	V	v	v	—	—
RMS	—	—	—	—	—	—	—	+	+	+

^aPositive in the peripherally situated sustentacular cells.
Abbreviations: MEA, middle ear adenoma; NE, neuroendocrine features; JTP, jugulotympanic paraganglioma; MEN, meningioma; AN, acoustic neuroma; ESPT, endolymphatic sac papillary tumor; RMS, rhabdomyosarcoma; CK, cytokeratin; EMA, epithelial membrane antigen; CG, chromogranin; SYN, synaptophysin; NSE, neuron-specific enolase; GFAP, glial fibrillary acidic protein; VIM, vimentin; DES, desmin; + = positive; — = negative; +/- = variably positive.
Source: From Ref. 202.

structures (Fig. 29). A paranuclear clear zone is not present. Cellular pleomorphism may be prominent, but mitotic figures are uncommon. The stromal component is sparse, and it may appear fibrous or myxoid.

Histochemical stains show the presence of intraluminal, but not intracytoplasmic, mucin-positive material. PAS-positive material is not present. On immunohistochemical evaluation (Table 4), the neoplastic cells are cytokeratin-positive, including diffusely positive for AE1/AE3, CAM 5.2, and CK7, and focal and weak CK20 reactivity (203). Neuroendocrine differentiation may be seen (see below), as is seen by chromogranin, synaptophysin, and neuron-specific enolase (NSE) immunoreactivity. Serotonin and human pancreatic polypeptide also may be present. S-100 protein and vimentin staining may be present. Desmin and actin are negative.

Middle Ear Adenomas with Neuroendocrine Differentiation. In some MEAs, the cells may have dispersed or stippled nuclear chromatin with the “salt and pepper” pattern seen in neuroendocrine tumors (Fig. 30) and/or demonstrate architectural characteristics seen in association with neuroendocrine neoplasms (e.g., ribbons, cords, organoid growth). Immunoreac-

tivity for one or more neuroendocrine markers, including chromogranin and synaptophysin, is present (Fig. 31) (Table 4). In addition, NSE, serotonin, and human pancreatic polypeptide also may be present. Despite the presence of vasoactive compounds in these tumors, carcinoid syndrome is extraordinarily rare in association with these middle ear neoplasms. These MEAs with neuroendocrine differentiation have been termed “carcinoid tumors of the middle ear”

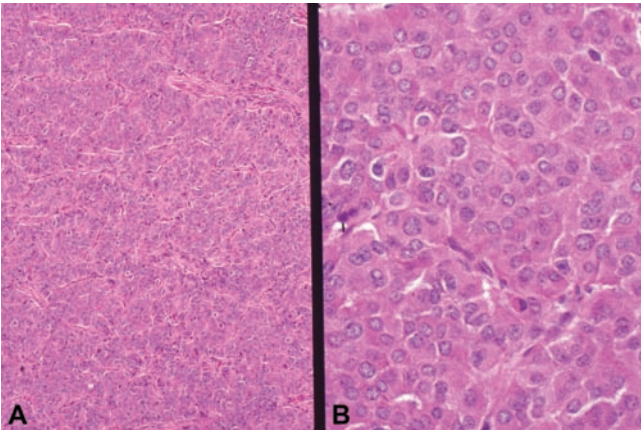


Figure 30 Middle ear adenoma with neuroendocrine differentiation showing (A) foci of solid cell nests with an organoid growth pattern and (B) nuclei with dispersed nuclear chromatin suggesting neuroendocrine differentiation.

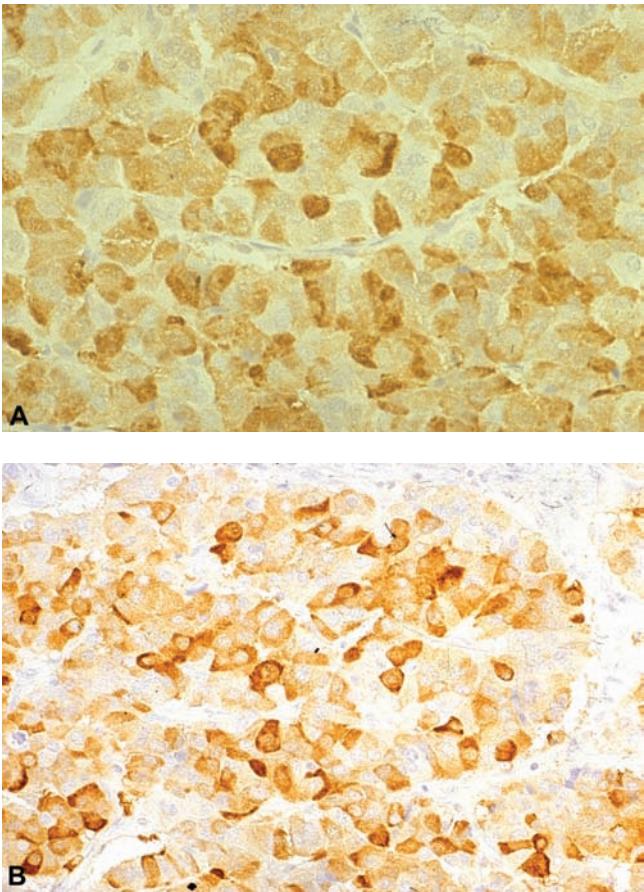


Figure 31 The immunoreactivity of middle ear adenomas with neuroendocrine differentiation include (A) chromogranin and (B) synaptophysin.

(203–207) as well as “neuroendocrine adenoma” (203). However, these carcinoid tumors are better viewed as part of the histological spectrum of MEA (208,209), albeit one with neuroendocrine differentiation, rather than as representing a distinct middle ear neoplasm separate from MEA. El-Naggar and colleagues (209) showed the presence of chromogranin-positive cells within hyperplastic but not in nonneoplastic middle ear epithelium overlying an MEA, which supports the inclusion of middle ear glandular tumors with neuroendocrine differentiation within the spectrum of MEA. Nevertheless, the issue whether to classify these tumors as MEA with neuroendocrine differentiation or carcinoid tumors (also referred to as well-differentiated neuroendocrine carcinomas) remains controversial. The controversy relates to the biological behavior of these tumors. On the basis of long-term follow-up, the overwhelming majority of these tumors have a benign biological course supporting the classification of these tumors as part of the histological spectrum of MEA, albeit with neuroendocrine differentiation, rather than representing a distinct middle ear neoplasm separate from MEA. However, Ramsey et al. (210) have reported two locally recurrent tumors (which may be a function of inadequate initial excision) with regional metastasis asserting that at least some of these middle ear neoplasms are carcinoid tumors/well-differentiated neuroendocrine carcinomas.

Differential Diagnosis

The differential diagnosis of MEA primarily includes jugulotympanic paraganglioma (JTP), meningioma, and acoustic neuroma (AN). The pathological and immunohistochemical features (Table 4) of these other tumor types are discussed in their respective sections. Glandular metaplasia may occur in the setting of COM. In contrast to MEA, the glandular proliferation in COM is focal or haphazardly arrayed, may show the presence of cilia (a feature not seen in MEA), and typically occurs in the presence of histological features of COM, including chronic inflammation with fibrosis and calcifications (tympanosclerosis). MEA may perforate the tympanic membrane, and it may appear to represent a neoplasm of the external auditory canal (Fig. 32), such as a ceruminous gland adenoma. The histological features of these two tumor types are distinctly different, so they should allow easy distinction. In contrast to the rare middle ear adenocarcinoma, MEA lacks marked cellular pleomorphism, increased mitotic activity, necrosis, or invasion of the bone and other soft tissue structures.

Some confusion exists in the literature regarding MEA and its relationship to the endolymphatic sac papillary tumor (ESPT). As is discussed later in this chapter, the pathological features and clinical course of ESPT differ decidedly from those of MEA.

Treatment and Prognosis

The treatment for all MEAs is complete surgical excision. Surgery may be conservative if the lesion is small and confined to the middle ear or more radical (mastoidectomy) for larger lesions associated with more

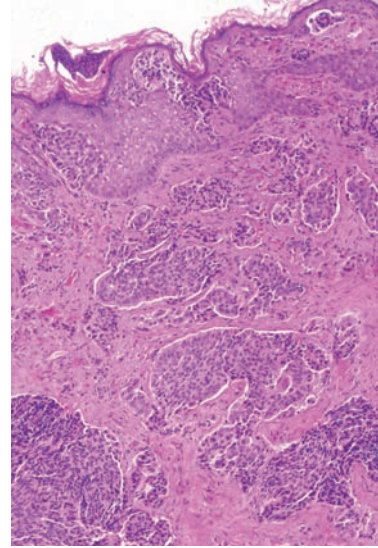


Figure 32 Middle ear adenoma that perforated the tympanic membrane presenting as an external auditory canal mass lesion. Given this history, the histological diagnosis of a ceruminous gland adenoma may be erroneously made. The histological features of middle ear adenoma and ceruminous gland adenoma are distinct, allowing for differentiation.

extensive structural involvement. Recurrent tumor may occur and is likely a function of inadequate excision. Some MEAs may be locally aggressive, and may rarely invade vital structures, causing death. In general, the clinical, radiological, and pathological findings are indicative of a benign tumor. The overwhelming majority of MEAs (with and without neuroendocrine differentiation) do not metastasize. However, as reported by Ramsey et al. (210), rare examples of MEAs with neuroendocrine differentiation may metastasize, raising the consideration that there are exceptional cases that may represent carcinoid tumors (also referred to as well-differentiated neuroendocrine carcinomas). The histological findings of MEAs with neuroendocrine differentiation reported to have metastasized are similar to ones that did not metastasize (210).

2. Jugulotympanic Paraganglioma

Clinical Features

JTP is a benign neoplasm that arises from the extra-adrenal neural crest-derived paraganglia specifically located in the middle ear or temporal bone region. Synonyms include glomus jugulare tumor or glomus tympanicum tumor.

JTPs are considered the most common tumors of the middle ear (200,201). They affect women more often than men, and they are most common in the fifth to seventh decades of life. The majority (85%) of JTPs arise in the jugular bulb, resulting in a mass lesion in the middle ear or external auditory canal (200). Approximately 12% originate from the Jacobson

nerve (tympanic branch of the glossopharyngeal nerve) and present as a middle ear tumor (200). Roughly, 3% begin from the Arnold nerve (posterior auricular branch of the vagus nerve) and arise in the external auditory canal (200). The most common symptom is conductive hearing loss. Other symptoms include tinnitus, fullness, otic discharge, pain, hemorrhage, facial nerve abnormalities, and vertigo. JTPs are often locally invasive neoplasms that destroy the adjacent structures, including the temporal bone and mastoid (200,211). Neurological abnormalities, including cranial nerve palsies, cerebellar dysfunction, dysphagia, and hoarseness, may be seen, and these relate to the invasive capabilities of this neoplasm.

Radiology

Computed tomography scan shows a soft tissue mass often with evidence of extensive destruction of adjacent structures. Since JTPs are vascularized lesions, carotid angiography will show the lesion fed by branches of nearby large arteries (211,212). By magnetic resonance imaging (MRI), tumors larger than 2 cm have a unique salt and pepper pattern of hyperintensity and hypointensity on T1-weighted and T2-weighted imaging (212).

Etiology

JTPs may be familial (213). Familial JTPs may be multifocal, including jugulotympanic and carotid body. An autosomal dominant pattern of inheritance is favored. Genetic analysis has shown linkage with two different loci, including 11q13.1 and 11q22.3-q23 (214,215).

Classification

Jugular and tympanic paragangliomas have been reported as a single entity (i.e., temporal bone paragangliomas), but their distinction has important clinical and therapeutic implications; as such, classification schemes on the basis of site of origin (Table 5) or on

Table 5 Classification of Temporal Bone Paragangliomas

Class A	Tumors arising along the tympanic plexus on the middle ear promontory
Class B	Tumors arising from the inferior tympanic canal of the hypotympanum; may invade the middle ear and mastoid; cortical bone over jugular bulb is intact; carotid canal is intact
Class C	Tumors arising in dome of jugular bulb and involving the overlying cortical bone
C1	Tumors eroding the carotid canal but not involving the carotid artery
C2	Tumors involving the vertical carotid canal
C3	Tumors involving the horizontal carotid canal; foramen lacerum is free of tumor
C4	Tumors involving the foramen lacerum and the cavernous sinus
Class D	Tumors with intracranial extension of posterior fossa
De1	Extradural tumor of <2 cm medial dural displacement
De2	Extradural tumor of >2 cm medial dural displacement
Di1	Intradural tumor of <2 cm
Di2	Intradural tumor of >2 cm
Di3	Neurosurgically unresectable tumor

Table 6 Glasscock–Jackson Classification of Glomus Tumors

Glomus tympanicum	
Type I	Small mass limited to promontory
Type II	Tumor completely filling the middle ear space
Type III	Tumor filling the middle ear and extending into the mastoid
Type IV	Tumor filling the middle ear, extending into the mastoid or through the tympanic membrane to fill the external auditory canal; may also extend anterior to the internal carotid artery
Glomus jugulare	
Type I	Small tumor involving the jugular bulb, middle ear, and mastoid
Type II	Tumor extending under the internal auditory canal; may have intracranial extension
Type III	Tumor extending into petrous apex; may have intracranial extension
Type IV	Tumor extending beyond the petrous apex into the clivus or infratemporal fossa; may have intracranial extension

the basis of site of origin and extent of tumor involvement have been developed (Table 6) (212).

Pathology

Gross. Grossly, JTPs are polypoid, red, friable masses that are identified behind an intact tympanic membrane or within the external auditory canal (Fig. 33). They vary in size from a few millimeters to a large mass that completely fills the middle ear space.

Microscopy. The histological appearance of all extra-adrenal paragangliomas is the same. The hallmark feature is the presence of cell nests or a so-called zellballen pattern (Fig. 34). The stroma surrounding and separating the nests is composed of prominent fibrovascular tissue. While this pattern is characteristic of paragangliomas, it can be seen in other tumors, including other neuroendocrine tumors, melanomas,

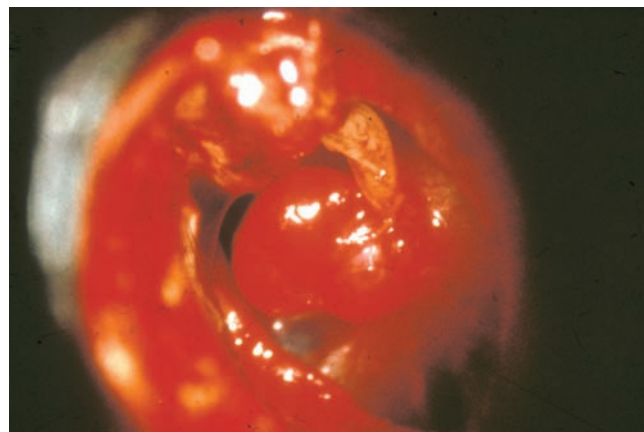


Figure 33 Jugulotympanic paraganglioma appearing as a polypoid, red mass that perforated the tympanic membrane and protruding into the external auditory canal from its origin in the middle ear.

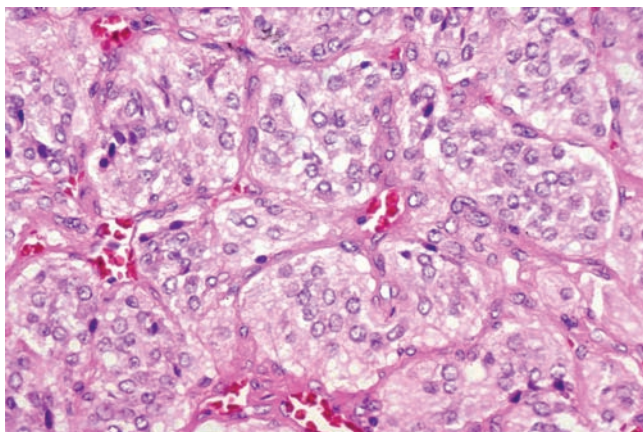


Figure 34 Jugulotympanic paraganglioma. This lesion shows the classic organoid or the cell nest growth pattern, including round or oval cells with uniform nuclei, a dispersed chromatin pattern, and abundant eosinophilic granular or vacuolated cytoplasm. The sustentacular cells are located at the periphery of the cell nests, but these are difficult to identify by light microscopy.

and carcinomas. Paragangliomas are predominantly composed of chief cells, which are round or oval cells with uniform nuclei; a dispersed chromatin pattern; and abundant eosinophilic, granular, or vacuolated cytoplasm. The sustentacular cells, which represent modified Schwann cells, are located at the periphery of the cell nests, appearing as spindle-shaped, basophilic cells, but these are difficult to identify by light microscopy. Cellular and nuclear pleomorphism can be seen, but these features are not indicative of malignancy. Mitotic figures and necrosis are infrequently identified. Paragangliomas lack glandular or alveolar differentiation.

The diagnosis of JTP is facilitated by immunohistochemical stains. The immunohistochemical profile includes chromogranin and synaptophysin positivity in the chief cells and S-100 protein staining localized to the peripheral sustentacular cells (Fig. 35). Vimentin is variably reactive in both the chief cells and sustentacular cells. Epithelial markers, including cytokeratin as well as HMB-45 and mesenchymal markers (desmin and other markers of myogenic differentiation) are negative. Rare examples of apparently cytokeratin-reactive paragangliomas have been reported (216). The ultrastructural evaluation shows the presence of neurosecretory granules (217).

Paragangliomas are often readily identified by light microscopical evaluation. However, in certain instances, they may be difficult to differentiate from other tumors. Not infrequently, middle ear and temporal paragangliomas do not show the characteristic cell nest appearance. This “loss” of the organoid growth may be artifactually induced by surgical manipulation (“squeezing”) of the tissue during removal (Fig. 36). The absence of the typical growth pattern may result in diagnostic confusion with other middle ear tumors (Fig. 36). In addition to the loss of

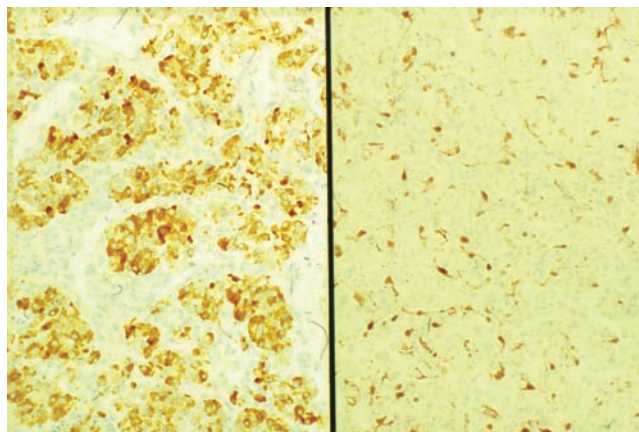


Figure 35 The immunohistochemical antigenic profile of all paragangliomas irrespective of site, including this jugulotympanic paraganglioma includes chromogranin positivity in the chief cells (*left*) and S-100 protein staining localized to the peripheral sustentacular cells (*right*).

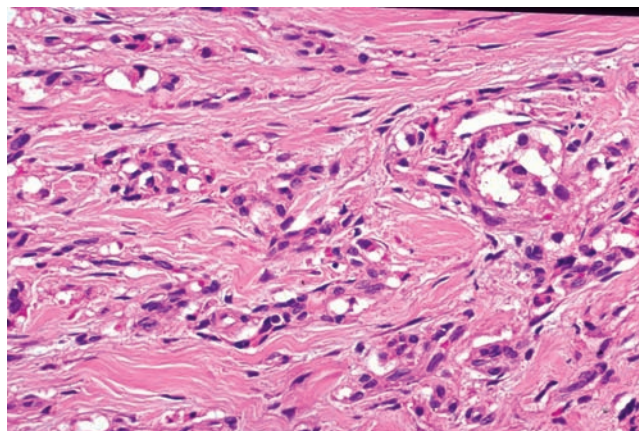


Figure 36 Jugulotympanic paraganglioma. The typical organoid growth pattern is absent, and the lesion is associated with densely fibrotic stroma. The absence of the typical light microscopical findings may suggest alternative diagnoses.

an organoid pattern of growth, JTPs may be associated with a dense fibrous stroma and an appearance of infiltrative growth. Special stains may aid in the diagnosis. Reticulin staining may better delineate the cell nest growth pattern, with staining of the fibrovascular cores surrounding the neoplastic nests (Fig. 37). In addition, the tumor cells are argyrophilic (Churukian—Schenk). Argentaffin (Fontana), mucicarmine, and PAS stains are negative. These findings may result in an erroneous interpretation as a malignant neoplasm. Typical immunoreactive staining patterns for chromogranin and S-100 protein should allow for a correct diagnosis.

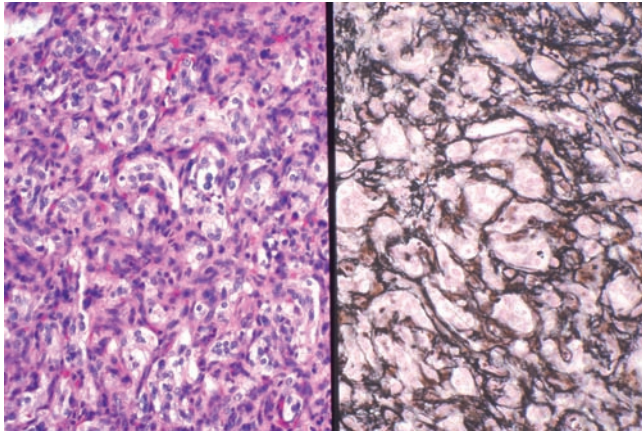


Figure 37 Jugulotympanic paraganglioma. The typical organoid growth pattern is obscured (*left*); reticulin stain is helpful in delineating the cell nest growth pattern (*right*).

Differential Diagnosis

The differential diagnosis of JTP primarily includes MEA, meningioma, and AN. If the histology is not distinctive in separating JTP from these other tumors, the immunohistochemical reactivity differentiates these tumors (Table 4).

Treatment and Prognosis

Complete surgical excision is the treatment of choice; however, the location and invasive nature of these lesions often preclude complete resection. Unresectable paragangliomas include those with extensive skull base involvement or intracranial extension, and patients who might be poor surgical candidates, including medically infirm and elderly. In such cases, radiation therapy is a useful adjunct to surgery. Radiotherapy results in a decrease or ablation of vascularity and promotes fibrosis. Radiotherapy has been primarily used to treat jugular paragangliomas of the temporal bone. As there is rarely total resolution of the tumor following radiotherapy, successful treatment of paragangliomas with radiotherapy is defined as local control in the form of stability or regression of tumor size and nonprogression or improvement of neurological symptoms (218,219). Preoperative embolization is useful in decreasing the vascularity of the tumor and facilitating surgical resection. Postembolization angiography should document absence of tumor “blush” with continued patency of the external carotid systems; not all paragangliomas should be embolized. The decision is dependent on the location and extent of tumor, and the experience of the surgeon and interventional radiologist. Local recurrences can be seen in up to 50% of cases. The histological appearance of paragangliomas does not correlate to the biological behavior of the tumor. Intracranial extension may occur in up to 15% of cases (220). Functioning JTPs, which are evidenced by endocrinopathic manifestations, occur, but they are extremely uncom-

mon. Malignant JTPs do occur; they are associated with histological criteria of malignancy, including increased mitotic activity; necrosis that is usually seen within the center of the cell nests; and vascular invasion, and they may metastasize to the cervical lymph nodes, lungs, and liver (221,222). In general, DNA ploidy studies by image analysis are not predictive of the behavior of paragangliomas (219).

3. Acoustic Neuroma

Clinical Features

AN is a benign neoplasm that originates from Schwann cells, specifically from cranial nerve VIII. Synonyms include neurilemoma, acoustic Schwannoma, and benign peripheral nerve sheath tumor.

AN accounts for up to 10% of all intracranial neoplasms and represents up to 90% of all cerebello-pontine angle tumors (200,201). ANs are more common in women than in men, and they may affect any age; they are, however, most common in the fourth to seventh decades of life. The majority of ANs involve the superior or vestibular portion rather than the cochlear portion of cranial nerve VIII. Symptoms include progressive (sensorineural) hearing loss, tinnitus, and loss of equilibrium. With progression, the tumor enlarges, and it may compress adjacent cranial nerves (V, VII, IX, X, XI), the cerebellum, and the brain stem, leading to facial paresthesia and numbness, headaches, nausea, vomiting, diplopia, and ataxia. Up to 8% may be bilateral (223–227), a potential indicator of neurofibromatosis type 2 (226,227).

Radiology

The radiological features of AN include flaring, asymmetric widening, or erosion of the internal auditory canal (200,201). Tumors as small as 1 cm or less are capable of being detected with CT or MRI.

Etiology

NF-2 is an autosomal dominant condition. The gene for NF-2 has been mapped to the long arm of chromosome 22 (22q12) (227). The hallmark of NF-2 is bilateral ANs (228). Patients with NF-2 also experience an increased incidence of multiple, separate-occurring meningiomas in intra- and extracranial sites. Symptoms of neurofibromatosis may be seen in up to 16% of patients and those with neurofibromatosis who develop ANs generally are symptomatic at an earlier age (2nd decade) and have a higher incidence of bilateral ANs. Patients with AN (or meningioma) who are younger than 30 years should raise concern for a diagnosis of NF-2.

Pathology

Gross. The gross appearance of AN includes a circumscribed, tan-white, rubbery-to-firm mass that may appear yellow and show cystic change. The tumor ranges in size from a few millimeters up to 4 to 5 cm at its greatest diameter.

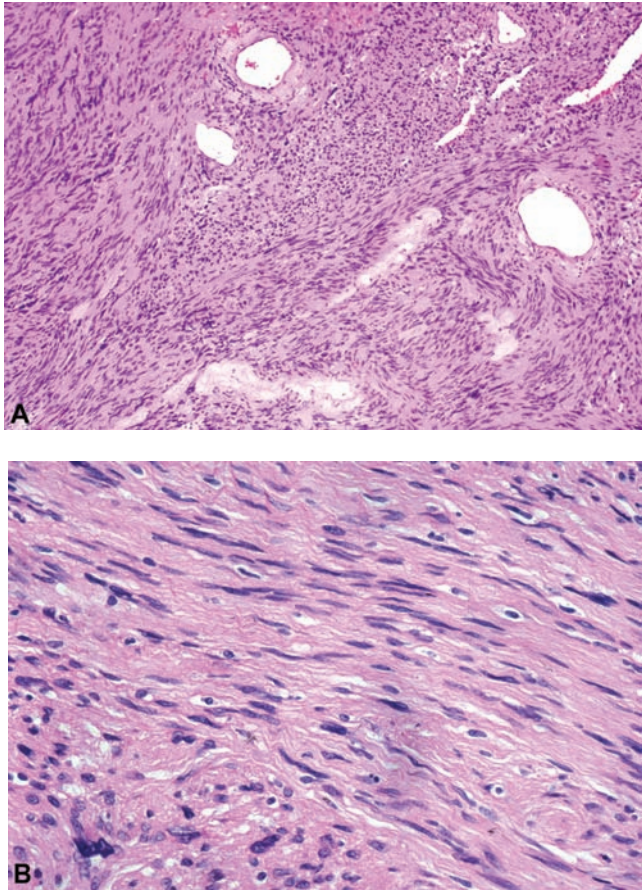


Figure 38 Acoustic neuroma. (A) The tumor is unencapsulated and has fascicular growth comprised of spindle-shaped cells; vascular hyalinization is present. (B) The cellular component includes elongated and twisted-appearing nuclei with indistinct cytoplasmic borders.

Microscopy. Histologically, the tumors are unencapsulated, and they are similar in appearance to benign schwannomas of all other locations. The cellular component includes elongated and twisted nuclei with indistinct cytoplasmic borders. The cells are arranged in short, interlacing fascicles, and whorling or palisading of nuclei called Verocay bodies may be seen (Fig. 38). The cellularity varies, and some benign schwannomas can be highly cellular (so-called cellular schwannoma). Mitotic figures are usually sparse in number. Cellular pleomorphism with hyperchromasia can be identified, but it is not a feature of malignancy. Retrogressive changes, including cystic degeneration, necrosis, hyalinization, calcification, and hemorrhage, may also be seen. Schwannomas have prominent vascularity composed of large vessels with thickened (hyalinized) walls.

Immunohistochemical staining shows the presence of diffuse, intense S-100 protein reactivity (Fig. 39). No immunoreactivity for cytokeratin or the neuroendocrine markers chromogranin and synaptophysin is present.

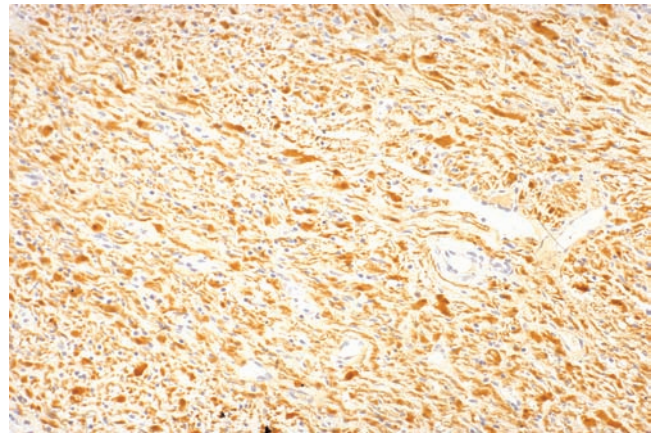


Figure 39 Acoustic neuroma. Diffuse and intense S-100 protein immunoreactivity is present.

Differential Diagnosis

The differential diagnosis includes MEA, JTP, and meningioma. The differentiation of these tumor types can be achieved by the light microscopical and immunohistochemical features for each tumor type (Table 4).

Treatment and Prognosis

Complete surgical excision is the treatment of choice, and it usually is curative. AN may result in death secondary to the herniation of the brain stem in patients with untreated or large neoplasms. Malignant ANs are exceedingly rare, and, if they are present, neurofibromatosis should be suspected.

4. Meningioma

Clinical Features

Meningiomas are benign neoplasms arising from arachnoid cells forming the arachnoid villi that are seen in relation to the dural sinuses.

Meningiomas represent from 13% to 18% of all intracranial tumors, and they are the second most common tumors of the cerebellopontine angle (200,201). Meningiomas are more common in women than in men, and they are most often seen in the fifth decade of life (229). They infrequently occur in children. The occurrence of a meningioma outside the CNS is considered ectopic, and it can be divided into those tumors with no identifiable CNS connection (primary) and those with a CNS connection (secondary). The development of primary meningiomas in the middle ear and temporal bone results either from direct extension or the presence of ectopic arachnoid cells. The middle ear and temporal bone are the most common sites of ectopically located meningiomas in the head and neck region. Sites of involvement include the internal auditory canal, jugular foramen, geniculate ganglion, the roof of the eustachian tube, and the sulcus

of the greater petrosal nerve (200). The clinical presentation of middle ear meningiomas includes progressive hearing loss, loss of equilibrium, headaches, cerebellar dysfunction, and cranial nerve abnormalities.

Etiology

Meningiomas may be associated with neurofibromatosis type 2. Mutations in the NF2 gene probably account for the formation of more than half of all meningiomas (230). Patients with NF-2 also experience increased incidence of multiple, separate-occurring meningiomas in intra- and extracranial sites. Patients with a meningioma (or AN) who are younger than 30 years should raise concern for a diagnosis of NF-2.

Radiology

The radiological findings include a soft tissue mass with variable vascularity. A pathognomonic feature for meningioma in this location is the presence of speckled calcification in a soft tissue mass (200).

Pathology

Microscopy. The histological features of middle ear and temporal bone meningioma are similar to their intracranial counterparts (Fig. 40). The immunohistochemical antigenic profile of meningiomas includes reactivity for EMA and vimentin (Fig. 41). In contrast to MEAs, meningiomas are generally nonreactive for cytokeratin, and, in contrast to JTPs, meningiomas are nonreactive for neuroendocrine markers (i.e., chromogranin and synaptophysin) (Table 4).

Differential Diagnosis

The differential diagnosis includes MEA, JTP, and AN. The differentiation of these tumor types can be

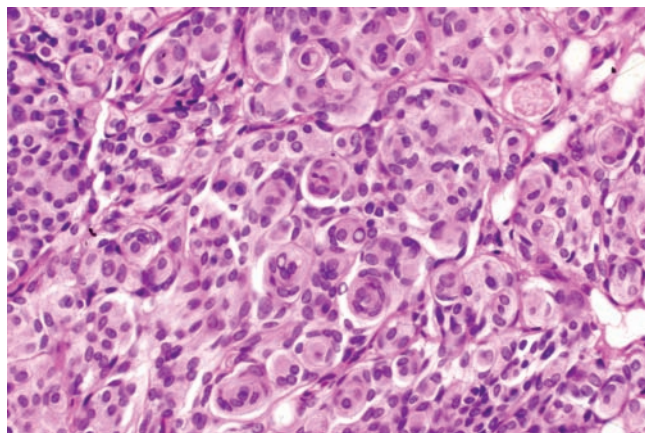


Figure 40 Meningioma of the internal auditory canal showing a cell nest or lobular growth separated by fibrovascular tissue. The cells are composed of round to oval or spindle-shaped nuclei with pale-staining cytoplasm and indistinct cell borders; the nuclei show a characteristic punched-out or empty appearance because of intranuclear cytoplasmic inclusions.

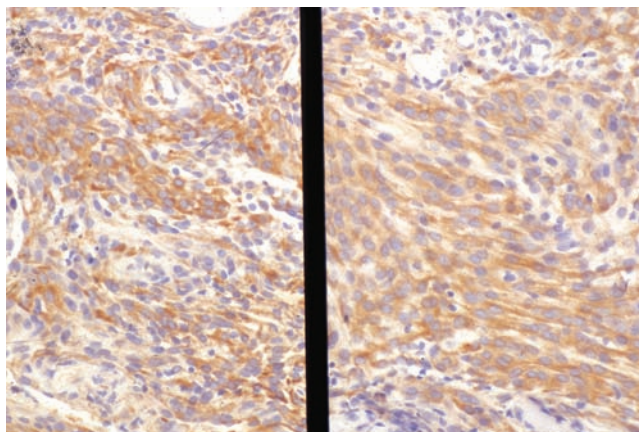


Figure 41 Immunoreactivity of meningiomas include epithelial membrane antigen (EMA) (*left*) and vimentin (*right*).

achieved by the light microscopical and immunohistochemical features for each tumor type (Table 4).

Treatment and Prognosis

Complete surgical excision is the treatment of choice, and it is curative. Malignant change rarely, if ever, occurs. A diagnosis of middle ear meningioma should be made only after clinical evaluation has excluded secondary extension from an intracranial neoplasm (231).

5. Other Benign Neoplasms of the Middle Ear and Temporal Bone

While uncommon, a number of other primary benign neoplasms can be found in the middle ear or temporal bone. Among these uncommon middle ear neoplasms are the Schneiderian-type mucosal papillomas of the middle ear, which are histologically identical to sinonasal or Schneiderian papillomas (232). Such neoplasms are more common in women than in men. They occur over a wide age range with an average age of occurrence in the fifth decade of life, and present with conductive hearing loss, otalgia, and otorrhea, and often occur in patients with a history of COM. Schneiderian-type mucosal papillomas of the middle ear arise *de novo* without evidence of sinonasal tract papillomas, although some have occurred in patients with sinonasal tract papillomas (232). Their histology is identical to that of inverted Schneiderian papillomas of the sinonasal tract (Fig. 42). Rarely, an associated SCC has been reported (232). Complete excision usually necessitating radical tympanomastoidectomy is the treatment of choice.

Other uncommon primary benign tumors of the middle ear and temporal bone are primarily mesenchymal, including hemangiomas (233–235), lipoma (236,237), osteoma (238–240), osteoblastoma (241), chondroblastoma (242), and teratomas (243).

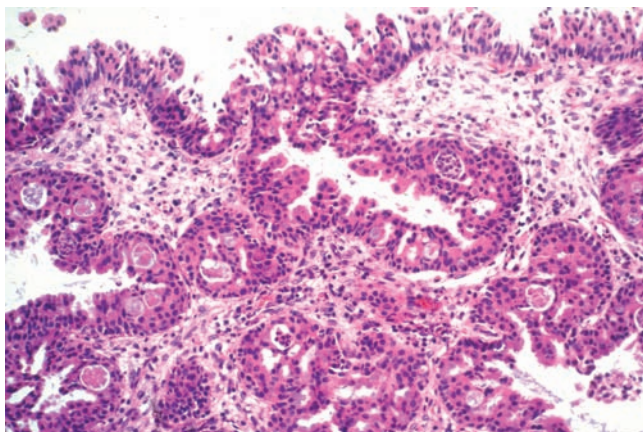


Figure 42 Middle ear papilloma with histological features of a sinonasal (Schneiderian)-type cylindrical cell papilloma.

C. Middle Ear and Temporal Bone Tumors of Indeterminant Biologic Behavior

1. Endolymphatic Sac Papillary Tumor

Clinical Features

The ESPT is an uncommon but distinct neoplasm that possibly is a manifestation of von Hippel–Lindau (VHL) syndrome (244,245). ESPT has had a variety of names, including adenoma of endolymphatic sac; adenoma and/or adenocarcinoma of temporal bone or mastoid; low-grade adenocarcinoma of probable endolymphatic sac origin; papillary adenoma of temporal bone; aggressive papillary tumor of temporal bone; aggressive papillary middle ear tumor; and, more recently, the Heffner tumor (246,247).

There is no gender predilection. ESPT occurs over a wide age range from the second to eighth decades of life. The most common symptom is unilateral hearing loss ranging from 6 months to 18 years; the hearing loss is most frequently sensorineural rather than conductive, but mixed types of hearing loss also occur. Other symptoms include tinnitus, vertigo, ataxia, and cranial nerve deficits.

Radiology

CT scan and MRI may show a lytic temporal bone lesion measuring from 4 to 6 cm (248). The center of the lesion most often is seen at or near the posterior-medial face of the petrous bone. Extension of tumor to the posterior cranial cavity has led to suggestions that the tumor took origin from the cerebellopontine angle; extension results in cerebellar involvement and evidence of compression and/or shifting of the fourth ventricle, brain stem, or pineal gland. Angiographic studies show a vascular or hypervascular lesion (244). The diagnosis of this tumor is based on clinical, radiographic, and pathological correlation.

Table 7 Neoplasms Associated with von Hippel–Lindau Syndrome

Retinal angiomas
Cerebellar and spinal hemangioblastomas
Endolymphatic sac papillary tumor
Renal cysts and cystadenomas
Pancreas: microcystic adenoma; endocrine tumors
Pheochromocytoma
Epididymal cyst and cystadenoma

Etiology

A diagnosis of ESPT should prompt the clinician to consider the possibility that the patient has VHL syndrome (244,245). VHL is an autosomal dominant disorder with variable expression. Tumor suppressor gene for VHL has been identified at chromosome 3p25–p26 (249). Patients with VHL have a predisposition to the development of numerous CNS and abdominal organ tumors (Table 7).

Histogenesis

An endolymphatic sac origin for these tumors is supported by the following: (i) early clinical manifestations of vestibular disease, including sensorineural hearing loss, tinnitus, and episodic vertigo; (ii) radiographic features showing a tumor in the posterior-medial petrous ridge, a site where the endolymphatic sac is located; (iii) identification of an in situ tumor (i. e., originating from within the endolymphatic sac); and (iv) the morphological, immunohistochemical, and ultrastructural similarities of the tumor with the normal endolymphatic sac epithelium (246).

Pathology

Microscopy. The histopathological appearance of ESPT is quite variable. The papillary structures are generally not complex in their growth. The neoplastic cells vary from flattened- or attenuated-appearing cells to columnar-appearing cells (Fig. 43). Most often, only a single row of cells is present. Occasionally, the surface epithelial cells may have an appearance that suggests a double layer of cells (epithelial and myoepithelial); however, the “outer” row of cells in all probability represents a stromal element, as these cells have not been shown to be immunoreactive with myoepithelial markers (248). The epithelial cells have uniform nuclei that are usually situated either in the center of the cells or toward the luminal aspect, and they have a pale eosinophilic- to clear-appearing cytoplasm. The latter may predominate in any given tumor. Cell borders may be seen, but, not infrequently, the neoplastic cells lack a distinct cell membrane. In some cases, hypercellular areas with crowded, variably sized cystic glandular spaces that contain eosinophilic (colloid-like) material are noted (Fig. 44). The latter appear remarkably similar to thyroid tissue. In all cases, pleomorphism is minimal, and mitotic activity and necrosis are rarely present.

A granulation tissue reaction is seen in association with the neoplastic cells, and it includes the small vascular spaces lying in close proximity to the surface

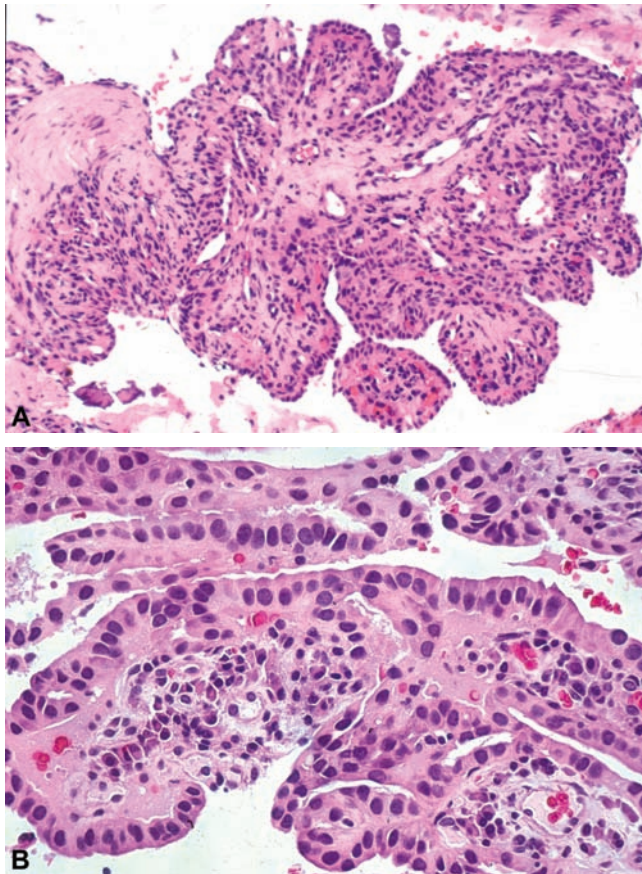


Figure 43 Endolymphatic sac papillary tumor. (A) The lesion is characterized by a papillary growth pattern. (B) In this example, the epithelial component is composed of a distinct layer of cuboidal- to columnar-appearing cells with delineated cell borders.

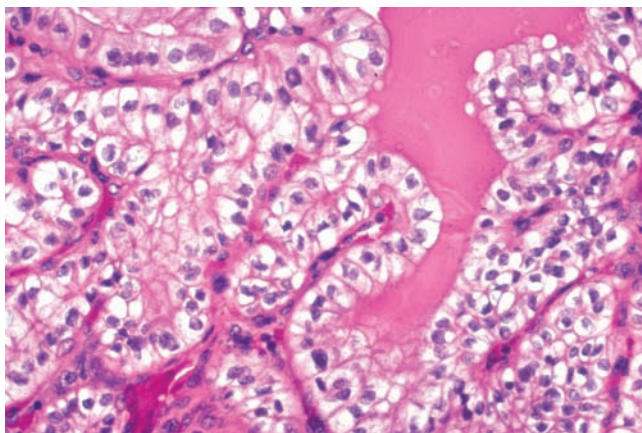


Figure 44 Endolymphatic sac papillary tumor. This inner ear tumor localized to the petrous apex shows the appearance of a thyroid lesion, including variably sized cystic spaces contain eosinophilic (colloid-like) material and nuclear alterations simulating those seen in association with thyroid papillary carcinoma. Thyroglobulin and thyroid transcription factor 1 staining were negative (not shown).

epithelium and/or within the stroma of the papillary fronds. Because of the absence of a distinct cell membrane around the neoplastic cells, a sharp demarcation separating the neoplastic cells from the subjacent granulation tissue is not observed. This appearance may create diagnostic confusion so that the neoplastic proliferation is not appreciated and the entire process is viewed as reactive. This interpretation is further enhanced by the stromal presence of a mixed inflammatory cell infiltrate, fibrosis, vascular proliferation, fresh hemorrhage, and/or hemosiderin (within the neoplastic cells or within macrophages), cholesterol granulomas, and dystrophic calcification. Dystrophic calcification does not include laminated calcific concretions (psammoma bodies).

Intracytoplasmic diastase-sensitive, PAS-positive material may be present. The colloid-like luminal material stains strongly with PAS either with or without diastase digestion. Intracytoplasmic and intraluminal mucin staining is rarely positive. Iron stains are positive. ESPTs are diffusely cytokeratin-positive, and they also show variable reactivity for EMA, S-100 protein, vimentin, NSE, GFAP, Ber-EP4, synaptophysin, and Leu-7 (Table 4). Thyroglobulin immunoreactivity is not seen. Ultrastructurally, ESPTs show the presence of intercellular junctional complexes, microvilli, basement membrane material, rough endoplasmic reticulum, intracytoplasmic glycogen, and secretory granules (248).

Differential Diagnosis

The differential diagnosis includes MEA. However, the clinical, radiographic, and pathological features that are unique to ESPT should allow for distinction. The same would apply for the other common neoplasms of the middle ear and temporal bone. The differential diagnosis also includes choroid plexus papilloma and metastatic carcinoma of thyroid or renal origin. Choroid plexus papillomas are intracranial (i.e., intraventricular) tumors with histological features that are different from those of ESPT (246). The absence of thyroglobulin reactivity and thyroid transcription factor 1 (TTF1) differentiates ESPT from metastatic thyroid papillary carcinoma. Metastatic renal cell carcinoma is immunoreactive for renal cell marker and CD10, markers not identified in ESPT. Further, the immunohistochemical antigenic features seen in ESPT are not found in renal cell carcinoma.

Treatment and Prognosis

Radical surgery, including mastoidectomy and temporal bone resection that may necessitate sacrifice of cranial nerves, is the treatment of choice, and it is potentially curative. Local recurrence results following inadequate surgical removal, and operative morbidity may be high. Despite its relatively slow growth, these neoplasms are capable of widespread infiltration and destruction, and they may be lethal (248). The prognosis is dependent on the extent of disease and the adequacy of the resection. Earlier detection when the tumors are relatively small and confined may decrease the operative-associated morbidity, and it may be curative.

D. Malignant Neoplasms of the External Ear and Auditory Canal

1. Basal Cell Carcinoma

Clinical Features

BCC is a slow growing, locally infiltrative malignant neoplasm of the skin and subcutaneous adnexal tissue. BCCs take origin from a pluripotential cell in either the basal cell layer of the surface epithelium or the epithelium of the subcutaneous adnexae.

BCC represents the most common cutaneous malignancy. BCC is more common in men than in women; generally, a tumor affecting adults and is most commonly seen in the seventh decade of life. The sun-exposed areas of the head and neck are the most frequent sites of occurrence. BCC may occur in virtually all cutaneous sites of the head and neck but among the more common locations include the nose, eyelids, nasolabial area, and the auricular area (pinna). In general, BCCs are asymptomatic; presentation usually occurs because the patient notices a growth. BCCs of the external auditory canal are uncommon (250). However, when this area is involved, it typically has extensive subcutaneous involvement, which may not be clinically appreciated (250).

Initially, the lesion is a raised papule or nodule with a waxy or translucent appearance covered by a fine capillary network (telangiectasia) (Fig. 45). With time, the central portion ulcerates and is surrounded by raised, pearly appearing borders, creating a typical papulonodular ulcerative lesion referred to as “rodent ulcer” (Fig. 45).

Etiology

The development of BCC is related to prolonged sun exposure with resulting actinic damage (251).

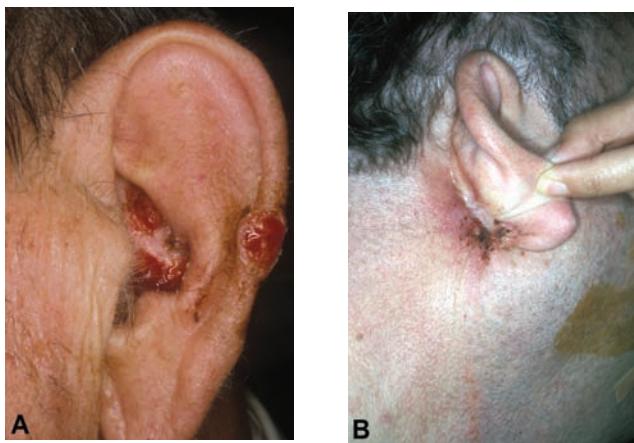


Figure 45 The clinical appearance of basal cell carcinoma of the external ear may include (A) a raised papule or nodule on the helix as well as involving the concha of the ear and (B) ulcerated lesion surrounded by raised borders, creating a papulonodular ulcerative (“rodent ulcer”) lesion on the cutaneous surface behind the ear. *Source:* Images courtesy of Mark Persky, M.D.

BCCs may be inherited in the autosomal dominant disorder called nevoid BCC syndrome caused by mutations in patched (PTCH), a tumor suppressor gene mapped to chromosome 9q22.3q31 (252,253). In few cases, the syndrome is due to a microdeletion at 9q22 (254,255). The nevoid BCC syndrome includes multiple BCCs most commonly involving the nose, mouth, eyes, and ear regions, occurrence in childhood, association with palmar and plantar pitting, odontogenic keratocysts of the jaws, skeletal developmental abnormalities (bifid ribs, brachymetacarpalism, and vertebral anomalies), ectopic calcification in dermal and soft tissue sites, and neurological abnormalities (mental retardation).

Pathology

See the chapter on diseases of the skin for a discussion of the pathology of BCCs.

Differential Diagnosis

See the chapter on diseases of the skin for a discussion of the differential diagnosis of BCCs.

Treatment and Prognosis

Complete surgical excision is the treatment of choice. Electrodesiccation and irradiation may be used, the latter particularly in cases that cannot be completely excised. The prognosis is excellent following complete excision. Local recurrence is not uncommon and is especially high in the morphea or sclerosing type of BCC. Metastases are rare except for neglected or long-standing tumors, which attain large size and become deeply and extensively infiltrative (256,257), as well as in association with the basosquamous (metatypical) carcinoma, which for all intents and purposes behaves as an SCC, including metastatic rates seen in approximately 7% of patients (258,259). This form of BCC requires a more aggressive surgical approach and a closer follow-up than other types of BCCs. When metastases occur, they usually spread to regional lymph nodes and to the lungs; metastatic disease is associated with poor prognosis irrespective of any therapeutic intervention. BCCs of the external auditory canal are notorious for extensive local invasion and extension to the middle ear, mastoid region, temporal bone, and potentially into the cranial cavity. For BCC of the external auditory canal, radical surgical excision may be necessary to eradicate tumors in this location (250).

2. Squamous Cell Carcinoma of the Ear, Including the Pinna and External Auditory Canal

Clinical Features

SCC accounts for approximately 25% of all SCCs of the head and neck, and 15% of all primary cutaneous carcinomas of external ear and auditory canal (260).

SCC of the external ear (i.e., auricular skin or pinna) is more common in men than in women and is most frequently seen in the sixth to eighth decades of life and presents as a nonhealing sore (261–263).

SCCs of the external auditory canal are more common in women than in men, most frequently seen in the sixth to seventh decades of life and present with symptoms mimicking those of COM, including pain, hearing deficits, and otorrhea (bloody or purulent) (261,262). Suspicion for the presence of a malignancy should be considered in patients with chronic ear infections who suddenly have a change in symptoms, including pain, bleeding, or facial paralysis.

SCCs of the external ear often are polypoid, rubbery to firm nodules that frequently have ulceration (Fig. 46). Given difficulties in their visualization due to location within the external auditory canal and concealment by purulent or hemorrhagic exudates, the gross characteristics of external auditory canal SCCs are not fully appreciated. Further, the extent of invasiveness may be underestimated on the basis of the gross appearance, making radiological assessment imperative in determining the extent of disease.

Radiology

Radiological assessment is helpful in the diagnosis of SCC of the external auditory canal. In the face of lesion that may appear to be limited to the canal belying its invasive nature, radiological imaging (e.g., CT scan) accurately assesses the extent of the tumor (264,265). Evidence of destruction of adjacent structures can be seen, including bone and other soft tissue structures, extension into the middle ear and growth into the middle cranial fossa, mastoid, and soft tissues beneath the temporal bone.

Pathology

See the chapter on diseases of the skin for a discussion of the pathology of SCCs.

Differential Diagnosis

Relative to external auditory canal SCCs, a key concern is differentiating SCC from SK, especially those SKs that are inflamed. Histologically, the diagnostic challenges in differentiation of SK from SCC may directly relate to limited tissue sampling as well as the presence of cytological atypia in SK that are irritated. The key differentiating feature is the absence (SK) or presence (SCC) of stromal invasion, which is not as simple to determine in practice as it is in theory. In equivocal cases, identification of lesion extent by radiological imaging may be the critical determinant in the diagnosis. Further, tissue sampling, including deeper tissues, is recommended. Presumptively, if tissue is sampled from deeper portions of the canal and/or deeper to the lesion itself, then the presence of squamous epithelium even with limited cytological atypia likely represents well-differentiated SCC, as such epithelia should not be expected to be so located in the setting of SK.

Treatment and Prognosis

For SCC of the external ear, complete surgical excision is the treatment of choice and/or radiotherapy. Con-

servative (limited) local resection can be performed for small lesions limited in extent without osseous invasion or invasion of the middle ear. Ogawa et al. (266) recommended radiotherapy in the treatment of early (T1) lesions. For advanced (higher stage) SCCs, more aggressive management is recommended, including radical surgical resection plus radiotherapy and/or chemotherapy (263,266–269). Elective parotidectomy for control of occult parotid node metastasis is necessary only in advanced SCC, whereas parotid management to secure adequate safety margins is mandatory for advanced SCC (270).

For SCC of the external auditory canal, complete surgical excision is the treatment of choice; this often requires a radical procedure (mastoidectomy or temporal bone resection). Radiotherapy may be indicated depending on the extent of disease. Prognosis is considered poor. SCCs in this location often go undetected for long periods of time and often present with advanced disease involving the mastoid and/or middle ear. In general, early detection and complete removal result in good prognosis (263,266–269). Nakagawa et al. (269) reported a three-year estimated survival for T1 and T2 lesions to be 100% and a five-year estimated survival for T3 and T4 to be 80% and 35%, respectively. Prognosis is dependent on the extent of disease (i.e., stage), completeness of surgery with tumor-free margins, recurrence, and metastasis (263,266–269). Local recurrence may occur in up to 25% of patients and may correlate with tumor size (268). Owing to the low risk of nodal metastasis occurring in less than 20% of patients (260,265,271–273), elective neck dissection is not advocated.

In a large study of SCCs of the skin by Rowe and colleagues (268), several pathological factors were linked to a propensity for local recurrence and metastases. These factors included a diameter greater than 2 cm, a depth greater than 4 mm, poor differentiation, perineural invasion, development within a scar, previously treated squamous carcinoma in the site, and host immunosuppression. Death is generally attributed to invasion of regional structures, particularly intracranial extension. Histological differentiation does not correlate with prognosis.

On the basis of clinical radiographic-histopathological correlation, a TNM staging system for external auditory meatus carcinoma was proposed (Tables 8 and 9) using preoperative CT and physical examination (274). Arriaga et al. (274) found two-year determinant survivals as follows: stage A, 100%; stage B, 50%; and stage C, 18%. Using the T system, Arriaga et al. (274) found mortality rates at two years to be as follows: T1 and T2, 0%; T3, 44%; and T4, 83%. More recently, Moody and colleagues (275) conducted a review of the staging system proposed by the University of Pittsburgh (274) for temporal bone cancer to evaluate survival status according to stage, treatment, and other certain prognostic factors. On the basis of T staging, these authors found that the two-year survival rates for primary SCC of the temporal bone were T1 lesions, 100%; T2, 80%; T3, 50%; and T4, 7%. Survival for T3 tumors was 75% with postoperative radiotherapy, compared with 0% with surgery alone.

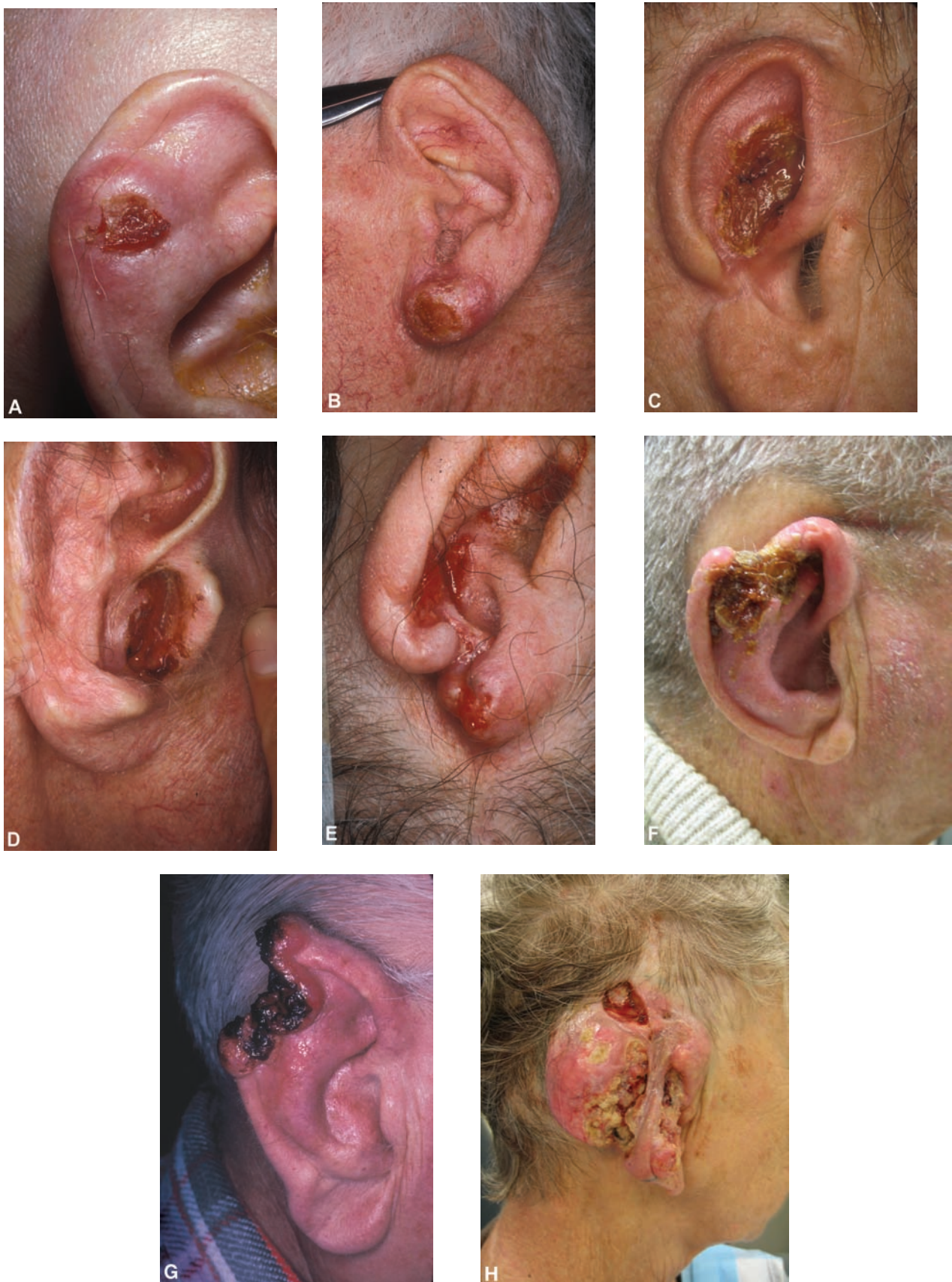


Figure 46 (A–H) The spectrum of clinical appearances of squamous cell carcinoma of the external ear involving a variety of primary sites on the pinna, as well as in the external auditory canal. *Source:* Images courtesy of Mark Persky, M.D.

Table 8 TNM Staging of Squamous Cell Carcinoma of the External Auditory Canal

Stage	Definition
A	Tumor limited to external auditory canal without erosion
B	Tumor eroding the osseous external auditory canal or involving the middle ear or mastoid, or both
C	Tumor involving the cochlea, dura, medial wall of the middle ear, petrous apex or surrounding soft tissue

Table 9 T Staging of Squamous Cell Carcinoma of the External Auditory Canal

Stage	Definition
T1	Tumor limited to external auditory canal without erosion of bone or extension into soft tissue
T2	Tumor with limited bone erosion (not full thickness) of the external auditory canal or radiographic evidence of limited (<0.5 cm) of soft tissue involvement (includes tumors extending through cartilaginous fissures or bone-cartilaginous junction of the external auditory canal)
T3	Tumor eroding the osseous external auditory canal (full thickness) with limited (<0.5 cm) of soft tissue involvement or tumor involving the middle ear or mastoid, or presentation with facial paralysis
T4	Tumor involving the cochlea, dura, medial wall of the middle ear, petrous apex or surrounding soft tissue

They concluded that the two-year survival data directly correlated with the staging system and that the use of adjuvant radiotherapy increased survival rate in patients with a T3 lesion (275).

3. Ceruminal Gland Adenocarcinoma

Clinical Features

Ceruminal gland adenocarcinoma is a malignant neoplasm of cerumen-secreting modified apocrine glands (ceruminal glands) located in the external auditory canal.

The demographics of ceruminal gland adenocarcinomas are similar to those of ceruminal gland adenomas. In contrast to ceruminal gland adenoma, patients with ceruminal gland adenocarcinomas have associated pain more often (276,277).

Pathology

Microscopy. Histologically, features that may assist in differentiating the ceruminal gland adenocarcinomas from the adenomas include a loss of the glandular double cell layer, with identification of only the inner or luminal epithelial cell, the presence of cell pleomorphism with nuclear anaplasia, increased mitotic activity, and invasive growth (Fig. 47). However, well-differentiated ceruminal gland adenocarcinomas may appear similar to their benign counterparts, and these are differentiated only on the basis of invasive growth. At the other end of the spectrum, poorly differentiated ceruminal adenocarcinomas do occur; these are recognized on the basis of their localization in the external auditory canal. In

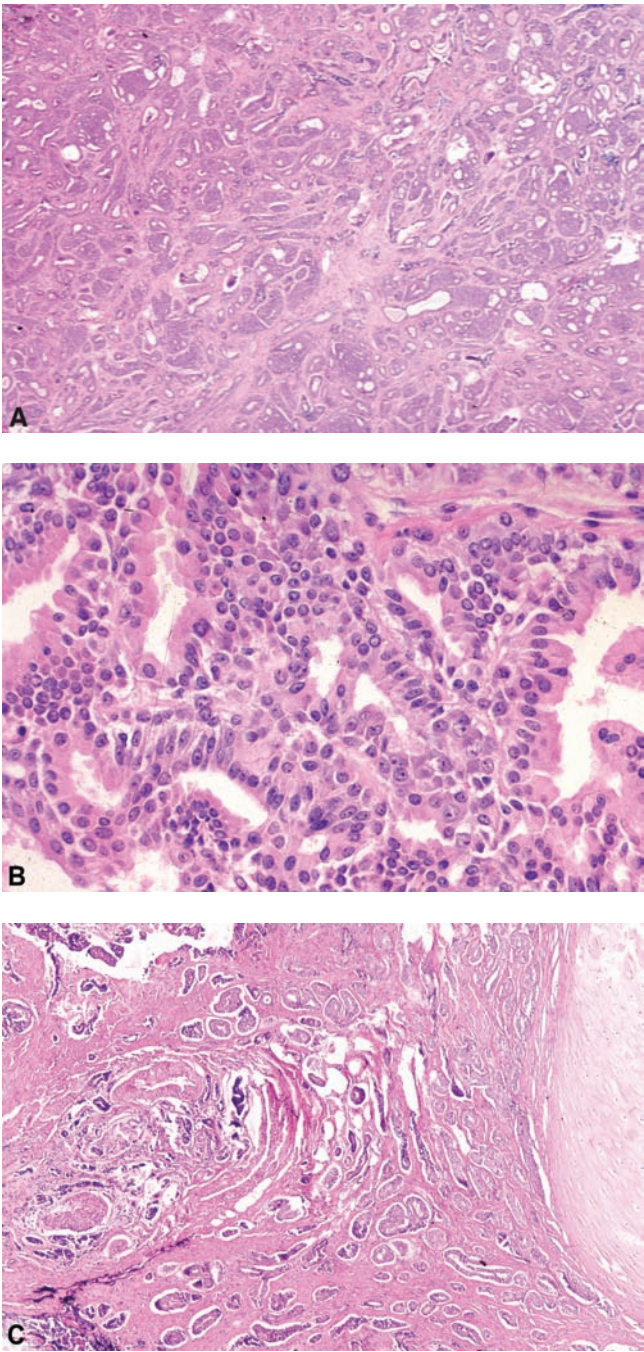


Figure 47 Ceruminal gland adenocarcinoma. (A) This external auditory canal glandular lesion is extensively infiltrative with a complex growth, including cribriform and solid patterns. (B) At higher magnification, the glands are characterized by the presence of cellular pleomorphism with nuclear anaplasia and by the loss of the dual cell layers seen in ceruminal gland adenomas, although on the outer aspects there is retention of apocrine type differentiation. (C) Perineural invasion and invasion of cartilage are present.

addition to the more “conventional” type of ceruminal gland adenocarcinomas, other types of ceruminal gland malignant tumors include adenoid cystic carcinoma and mucoepidermoid carcinoma. These tumors

are morphologically identical to their salivary gland counterparts.

Differential Diagnosis

Given the proximity of the parotid gland to the external auditory canal, the differential diagnosis for ceruminous gland adenoid cystic carcinoma and mucoepidermoid carcinoma includes the direct extension of similar tumors of primary parotid origin. Therefore, parotid gland adenoid cystic carcinoma and mucoepidermoid carcinoma should be excluded before such tumors are diagnosed as being of primary ceruminous gland origin. The same applies for ceruminous gland pleomorphic adenoma. Wolf and associates (192) have also cautioned about misdiagnosing a benign dermal eccrine cylindroma of the external auditory canal as an adenoid cystic carcinoma.

Treatment and Prognosis

For ceruminous gland adenocarcinoma, en bloc surgical resection is the treatment of choice. Middle ear or temporal bone involvement necessitates more radical surgery (276). Supplemental radiation therapy is recommended. Metastases are rare, and they include regional lymph nodes and the lung (191,276). For ceruminous gland adenoid cystic carcinoma and mucoepidermoid carcinoma, wide surgical resection with or without supplemental radiation therapy is the recommended treatment (277). The prognosis for ceruminous gland adenoid cystic carcinoma generally is similar to its salivary gland counterpart, including relatively good short-term survival (i.e., 5-year survival) but poor long-term survival (i.e., 10- to 20-year survival) (276,277).

4. Atypical Fibroxanthoma (Pleomorphic Undifferentiated Sarcoma of Skin)

Clinical Features

Atypical fibroxanthoma (AFX) is a pleomorphic, predominantly dermal mesenchymal tumor found primarily on actinic-damaged cutaneous sites of older patients or occasionally in younger patients involving the superficial soft tissues of the extremities and trunk (278). Synonyms have included superficial (low grade) MFH, pseudosarcoma of skin, and pseudosarcomatous dermatofibroma.

AFX occurs in two clinical forms, neither having a specific gender predilection. The most common form, accounting for approximately 75% of cases, affects elderly patients and commonly involves the head and neck (ears, cheeks, nose). A less common form, accounting for approximately 25% of cases, affects younger patients, commonly involving superficial sites on the limbs and trunk. However, more recently, the latter form of AFX is now thought to represent atypical fibrous histiocytomas (278). AFX most often presents as an asymptomatic solitary growth on the affected body site (Fig. 48). Patients may complain of bleeding, pruritus, and pain.

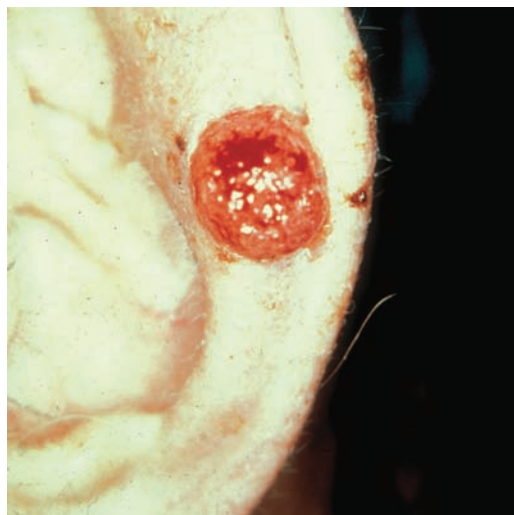


Figure 48 Atypical fibroxanthoma (AFX) of the external ear appearing as a solitary, delineated polypoid mass.

Etiology

The etiology is related to actinic damage. The presence of p53 mutations supports the role of ultraviolet radiation damage in the development of AFX (279). Therapeutic irradiation is also considered a predisposing factor in the development of AFX. Latent periods between radiation exposure and the development of AFX being more than 10 years represent an appropriate interval for a radiation-induced neoplasm (278).

Pathology

Gross. AFX of the ear presents as an asymptomatic, firm nodule measuring from 1 to 2 cm in diameter, often associated with ulceration.

Microscopy. Histologically, AFX is an unencapsulated, but generally circumscribed, spindle cell neoplasm arising in the dermis. The cellular component is varied, including a spectrum of elongated spindle-shaped to pleomorphic cells with hyperchromatic nuclei and bizarre multinucleated cells (Fig. 49). The larger cells may have foamy cytoplasm and are reminiscent of lipid-rich histiocytic cells. In some AFXs, a pleomorphic component may be absent and the tumors appear as a predominantly spindle cell, non-pleomorphic lesion (280). Increased mitotic figures, including atypical forms, are readily identified. Areas may exhibit a storiform pattern, but this is not usually prominent. Junctional activity is absent. Superficial areas adjacent to the tumor show solar elastosis and vascular proliferation; prominent stromal sclerosis may be present (281). A chronic inflammatory infiltrate may present. Vascular invasion may be seen, but necrosis is uncommon.

Unusual variants include clear cell and granular cell (282,283). The clear cell variant of AFX is characterized by sheets of large cells with foamy cytoplasm

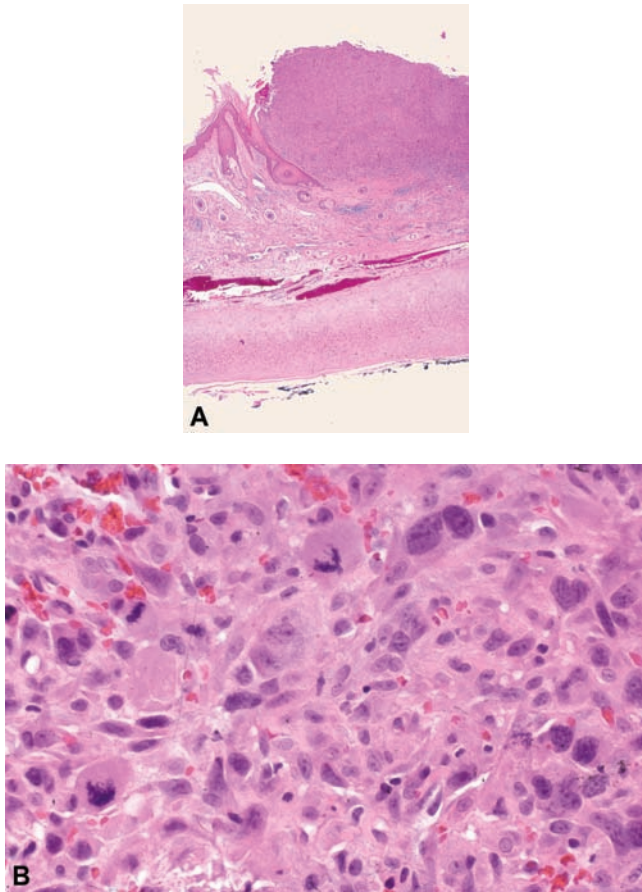


Figure 49 Atypical fibroxanthoma (AFX) of the ear. (A) An ulcerated, circumscribed cellular lesion is seen in the superficial aspect of the auricular skin. (B) The cellular component includes markedly pleomorphic cells with hyperchromatic nuclei, bizarre multinucleated cells, and increased mitotic figures, including atypical mitoses. Cells with foamy-appearing cytoplasm that are reminiscent of lipid-rich histiocytic cells are present.

and hyperchromatic, polypoid nuclei with frequent mitoses, including atypical mitoses (282). The clear cells express CD68 but not CD3, CD20, CD34, S-100 protein, muscle-specific actin, factor XIIIa, Melan-A, carcinoembryonic antigen, or cytokeratin (282). Differentiation from balloon cell melanoma, sebaceous carcinoma, pleomorphic liposarcoma, chordoma, parachordoma, tricholemmal carcinoma, and clear cell SCC depend on appropriate immunohistochemical stains.

Multinucleated, “osteoclastic-like” giant cells as well as osteoid may rarely be present (284). Uncommonly, pigmentation may occur. These lesions have been termed “pigmented atypical fibroxanthoma” (285). Pigmented AFX can be easily mistaken for malignant melanoma, clinically and histopathologically. The pigmentation is felt to represent hemorrhage, with neoplastic cells ingesting and degrading erythrocytes following intratumoral hemorrhage and accumulation of hemosiderin in their cytoplasm; the pigment stains for iron.

Immunohistochemistry is extremely valuable in the differential diagnosis of AFX. In AFX, there is variable staining for CD68 (KP1), muscle-specific actin, and smooth muscle actin (286,287). CD99 reactivity is present (288). No immunoreactivity is seen for cytokeratins, S-100 protein (except for scattered non-neoplastic dendritic cells), desmin, and melanoma markers (e.g., HMB-45, Melan-A) (280,286,287). Aberrant HMB-45 and MART-1 (melanoma antigen recognized by T cells-1) staining have been reported limited to the large, multinucleated cells with vacuolated cytoplasm (289). Ultrastructural studies have shown evidence of fibrohistiocytic and myofibroblastic features and, to a lesser extent, features of Langerhans’ cells (290). Features indicative of epithelial differentiation (e.g., prominent intercellular bridges, tonofibrils) or melanocytic differentiation (e.g., premelanosome, melanosomes) are absent.

Deletions on chromosomes 9p and 13q have been identified representing similar genetic alterations as seen in undifferentiated high-grade pleomorphic sarcoma, suggesting common pathogenetic pathway (291). However, statistically significant differences of genetic alterations between AFX and undifferentiated high-grade pleomorphic sarcoma concerning deletions on 1q, 3p, 5q, 11p, and 11q, gains on 7q and 12q, and high-level gains on 5p and 11q have been found (291). In addition, the absence of H-ras and K-ras mutations in AFX compared to undifferentiated pleomorphic sarcoma (MFH) have been reported (292). These genetic differences may contribute to the different biological behavior of these two tumors.

Differential Diagnosis

The differential diagnosis of AFX includes spindle cell squamous carcinoma and spindle cell malignant melanoma. This distinction has been previously discussed above. AFX must be differentiated from leiomyosarcoma. Immunohistochemical stains should allow the pathologist to separate AFX from leiomyosarcoma, with the latter tumor showing reactivity for desmin (289). The relationship of AFX to superficial MFH may be academic as both are associated with a good prognosis following complete surgical resection (293). If a tumor has the histological features of AFX but is large (>2 cm in diameter) and extensively infiltrative and has necrosis or vascular invasion, then it should be considered an MFH (278). This distinction is important as therapy for MFH includes surgery with supplemental irradiation.

Treatment and Prognosis

Conservative but complete surgical excision is the treatment of choice. The prognosis is excellent. Local recurrence, which is uncommon, is related to incomplete excision. Recurrent tumors may present as a large mass in the deep soft tissue, and these neoplasms should be considered and treated as a bona fide MFH (278). AFX have been reported to metastasize, but these cases may, in fact, represent MFH (278).

E. Malignant Neoplasms of the Middle Ear

1. Middle Ear Squamous Cell Carcinoma

Clinical Features

Middle ear SCC is a rare primary malignant neoplasm with squamous differentiation that originates from the middle ear mucosal epithelium.^(294,293) Middle ear SCC (ME-SCC) is most common in the sixth to seventh decades of life. There is no gender predilection. The majority of patients have a long history of COM, which is usually longer than 20 years. Early symptoms include pain with radiation to the scalp and face and hearing impairment. Late symptoms include facial palsies and vertigo. ME-SCC should be suspected in patients with long-standing COM who suddenly present with pain out of proportion to the clinical extent of disease and/or with an onset or increase of otorrhea that is often hemorrhagic and/or in those patients in whom clinical resolution following therapeutic doses of antibiotics is lacking.

Etiology

The development of ME-SCC is also linked to radiation treatment for intracranial neoplasms and radiation therapy for middle ear inflammatory conditions, although the latter is no longer used. High-risk human papillomavirus types 16 and 18 identified in ME-SCC raises HPV as a possible etiological factor, although a direct cause and effect has not been established⁽²⁹⁵⁾. Although concomitant cholesteatomas can be seen in up to 25% of cases, there is no correlation between cholesteatomas and the development of an ME-SCC.

Pathology

Microscopy. The histology of ME-SCC is similar to that of squamous carcinomas of other sites. The tumors vary from well to poorly differentiated, and they include infiltrative malignant cells with associated keratinization and/or intercellular bridges (Fig. 50). A background of COM, including chronic inflammation, tympanosclerosis, glandular metaplasia, and fibrosis, can be identified.

Differential Diagnosis

The differential diagnosis includes cholesteatoma and metastatic SCC. Cholesteatomas are characterized by the presence of keratinizing squamous epithelium lacking prominent rete pegs and an absence of dysplastic cytological changes. In contrast, SCC (even well-differentiated cancers) has dysplastic cytological changes, increased mitotic activity, and possibly dyskeratotic cells. Further, in adequately sampled tissue, an infiltrative growth with associated desmoplasia and scattered irregular shaped nests of squamous epithelium is a growth pattern not seen in cholesteatomas.

Metastatic SCC from a distant site must also be considered. Alternatively, a cutaneous SCC from an adjacent site (e.g., external ear, nasopharynx, parotid gland, skin) can directly invade the middle ear or temporal bone. These possibilities must be excluded before accepting an SCC as primary in the middle ear.

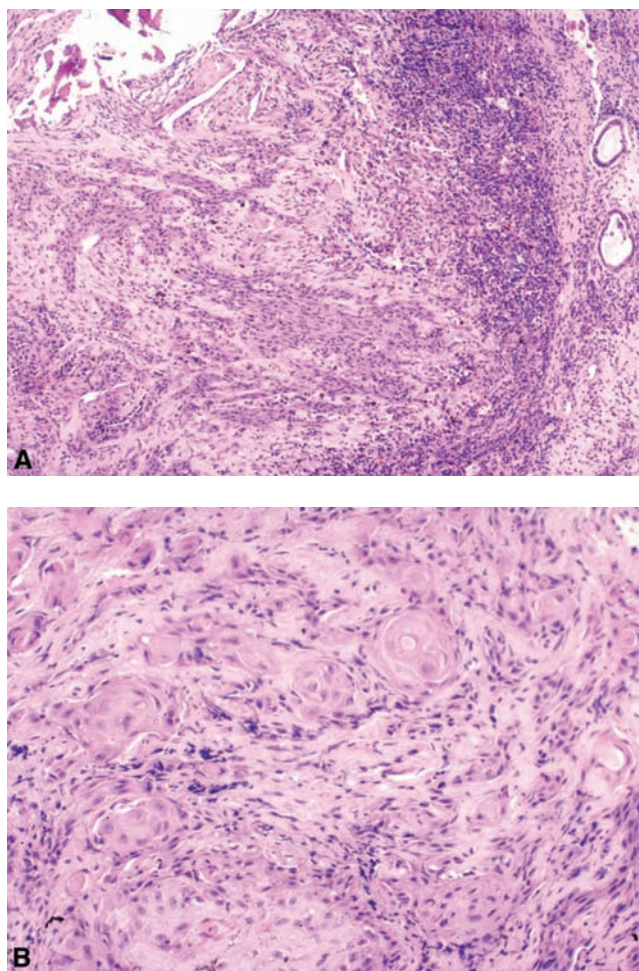


Figure 50 Squamous cell carcinoma of the middle ear. (A) Infiltrative nests and cords of squamous epithelium is present in association with histological findings of chronic otitis media, including dense inflammatory cell infiltrate, glandular metaplasia, and tympanosclerotic foci. (B) At higher magnification, their nests are irregularly shaped with associated nuclear pleomorphism and hyperchromasia and keratinization. The findings are those of a well-differentiated keratinizing squamous cell carcinoma arising in the background of chronic otitis media.

Treatment and Prognosis

Radical surgery (i.e., radical mastoidectomy, temporal bone resection) with postoperative radiation therapy is the treatment of choice. In advanced disease, chemotherapy may be beneficial. The prognosis has generally been poor with 5- and 10-year survival rates of 39% and 21%, respectively⁽²⁹⁴⁾. More recently, Moore et al.⁽²⁹⁶⁾ reported a five-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) of 77%, 79%, and 52%, respectively. These authors found that upfront complete resection (i.e., lateral temporal bone resection) when combined with postoperative radiation therapy may improve survival and decrease recurrence. They reported an improved OS, DSS, and DFS ($p < 0.004$ for each) and

reduced local recurrence ($p < 0.001$). While combined radical surgery and radiotherapy are the preferred treatment modalities for ME-SCC, Pemberton et al. (297) reported that radical radiotherapy (55 Gy in 20 daily fractions) alone achieves comparable results in terms of local control and cancer-specific survival and is a viable option in the treatment of ME-SCC. Metastatic disease from ME-SCC may occur, but is considered uncommon.

2. Middle Ear Adenocarcinoma

Clinical Features

Middle ear adenocarcinomas are extremely rare malignant glandular neoplasms arising from the middle ear mucosa (298). Middle ear adenocarcinomas have no gender predilection and occur over a wide age range between the second to sixth decades of life. Symptoms are typically present for many years and include progressive hearing loss and a unilateral draining ear; pain and vestibular manifestations are uncommon. Otoscopic examination in the majority of cases will identify an intact tympanic membrane with tumor confined to the middle ear space with possible extension to the mastoid; occasionally, and similar to the MEA, the adenocarcinoma will perforate through the tympanic membrane with extension into and presentation as an external auditory canal mass. Middle ear adenocarcinomas may attain a large size, filling the middle ear space and encasing the ossicles.

Etiology

The etiology for middle ear adenocarcinoma is unknown. There is no association between COM and the development of these adenocarcinomas.

Pathology

Gross. Variation in appearance ranges from gray-white to red-brown, rubbery to firm, and spongy to cystic. The neoplasm may attain large sizes filling the middle ear space and encasing the ossicles.

Microscopy. Histologically, middle ear adenocarcinomas are similar in many respects to MEAs. Like MEAs, adenocarcinomas are unencapsulated glandular lesions in which there is a diffuse glandular proliferation, including complex gland-in-gland (cribriform) growth. Typically, mucocytes are not identified. In contrast to adenomas, adenocarcinomas show the presence of marked nuclear pleomorphism with increased mitotic activity and infiltrative growth (Fig. 51). The latter includes invasion of soft tissue structures with perineural and perivascular invasion, and invasion of bone. A papillary and cystic variant (papillary cystadenocarcinoma) lined by cells with hyperchromatic nuclei and vacuolated cytoplasm can be identified.

Histochemical stains for epithelial mucin show the presence of intraluminal but not intracytoplasmic mucin-positive material. Lesional cells are immunoreactive for cytokeratins and epithelial membrane antigen. Immunoreactivity is not identified for neuroendocrine markers, for organ-specific markers, and/or for markers reactive in other adenocarcinomas as might be seen in metastatic carcinomas such as those of thyroid origin (thyroglobulin and TTF-1), prostate origin (prostate-specific antigen and prostatic acid phosphatase), renal origin (renal cell marker and CD10), and breast origin (BRST-2).

Differential Diagnosis

The differential diagnosis includes MEA and metastatic adenocarcinoma. Differentiation from MEA is based on light microscopical features (see above).

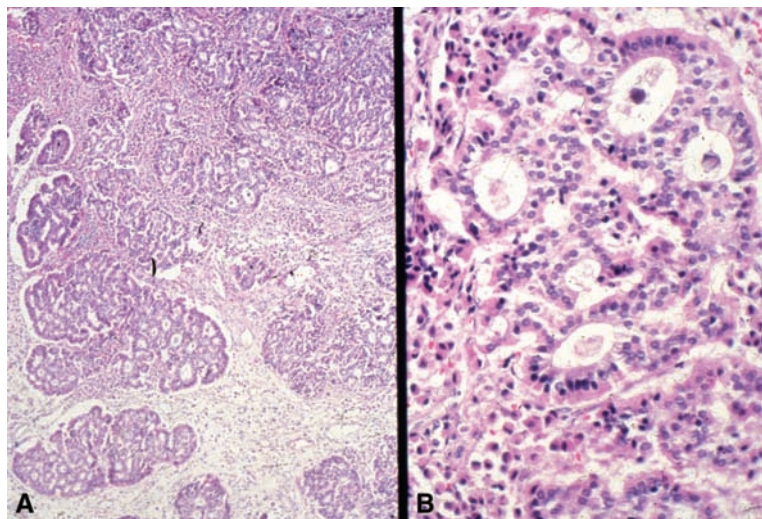


Figure 51 Middle ear adenocarcinoma. (A) Infiltrating glandular neoplasm showing complex growth pattern (left). (B) At higher magnification, the tumor complexity of growth is evident, including cribriform or back-to-back pattern with cellular pleomorphism.

Before rendering a diagnosis of primary middle ear adenocarcinoma, a metastasis to this region from a separate primary adenocarcinoma should be excluded. Metastases to the middle ear and temporal bone can be seen from virtually all sites but are most common from the breast, lungs, and kidneys. Clinical history and immunohistochemical staining should allow for this differentiation.

Treatment and Prognosis

Complete surgical excision is the treatment of choice. In general, these are slow-growing neoplasms that are locally aggressive but do not metastasize. Death may occur as a result of direct intracranial extension (298).

3. Other Malignant Tumors of the Middle Ear and Temporal Bone

While uncommon, a number of other malignant tumors can originate in the middle ear or temporal bone. These tumors are primarily of mesenchymal origin, including matrix forming such as osteosarcoma and chondrosarcoma. Osteosarcomas of the skull, including the temporal bone, are uncommon with only approximately 1% to 2% of all osteosarcomas occurring in this location (299). In this setting, osteosarcomas often arise in the setting of Paget disease of bone, fibrous dysplasia, or secondary to radiotherapy (299). Osteosarcomas of the skull are aggressive tumors with a tendency to metastasize to the lungs and brain and with a five-year survival of less than 15% (300,301). Chondrosarcomas of the temporal bone are rare. The petrous apex and posteromedial aspect of the temporal bone are perhaps the most common sites of occurrence (302). Chondrosarcomas of the temporal bone are not necessarily lethal tumors as with one study reporting 76% DFS over periods ranging up to eight years (302).

Other malignancies of the middle ear and temporal bones include hematolymphoid lesions, including malignant lymphomas (non-Hodgkins and Hodgkins), leukemia, and plasma cell dyscrasias (303). Middle ear and temporal bone involvement by a malignant hematolymphoid neoplasm often is secondary to primary disease elsewhere.

4. Metastatic Tumors to the Middle Ear and Temporal Bone (Secondary Tumors)

Metastatic tumors secondarily involving the middle ear and temporal bone originate from virtually every site. The more common malignant tumors to metastasize to this region originate from the breast, head and neck, lungs, and prostate (Fig. 52) (304). Other tumors that may metastasize to this region include malignant melanoma, thyroid carcinomas, and renal cell carcinoma (304). While metastases to the temporal bone often occur late in the disease course, metastatic involvement of the temporal bone may represent the initial presentation of a distant malignant disease. Metastatic disease to the temporal bone occurs via hematogenous spread but may also occur by direct extension from a

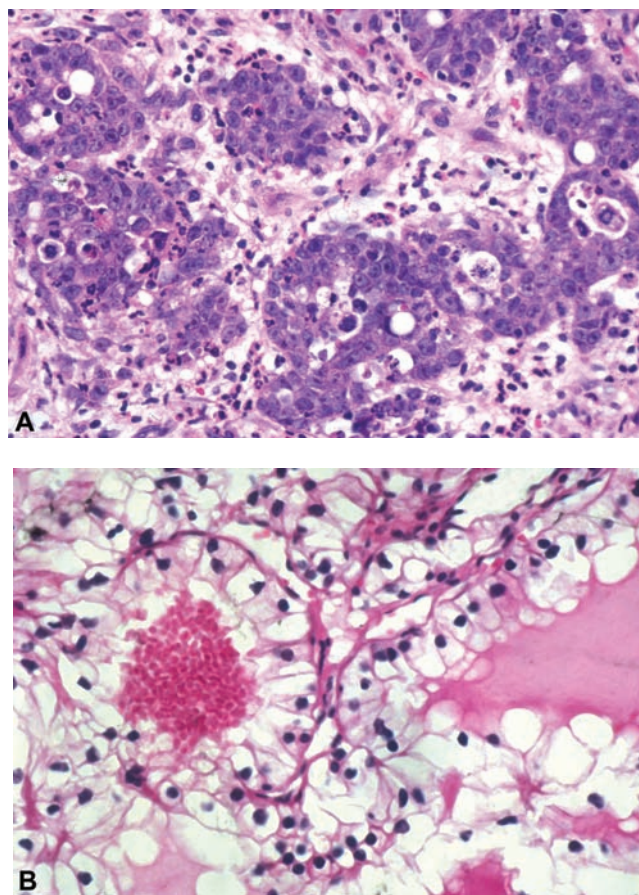


Figure 52 Metastatic disease to the ear and temporal bone may include (A) prostatic adenocarcinoma (confirmed immunoreactivity with prostate markers, not shown) and (B) renal cell carcinoma (confirmed immunoreactivity with CD10 and renal cell marker, not shown). In both examples, the primary carcinoma was not known, but once the diagnosis was suggested on the basis of light microscopic and immunohistochemical findings associated with the temporal bone lesions, respective primary carcinomas in the prostate and kidney were found.

nearby primary tumor (e.g., SCC), meningeal carcinomatosis, or leptomeningeal extension from an intracranial primary neoplasm.

REFERENCES

1. Hollinshead WH. The ear. In: Hollinshead WH, ed. *Anatomy for Surgeons*. 3rd ed. Philadelphia: Harper and Row, 1982:159–221.
2. Moore KL, Persaud TVN. The eye and ear. In: Moore ML, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 7th ed. Philadelphia: Saunders, 2003:465–483.
3. Dayal VS, Farkashidy J, Kokshanian A. Embryology of the ear. *Can J Otolaryngol* 1973; 2:136–142.
4. Schuknecht HF. Anatomy. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:31–74.

5. Nager GT. Anatomy. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1993:3-187.
6. Wenig BM, Michaels LM. The ear and temporal bone. In: Mills SE, ed. *Histology for Pathologists*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2007:371-401.
7. Baloh RW, Honrubia V. Vestibular physiology. In: Cummings CW, Frederickson JM, Harker LA, et al., eds. *Otolaryngology Head Neck Surgery*. 3rd ed. St. Louis: Mosby, 1998:2584-2622.
8. Lysakowski A, McCrea RA, Tomlinson RD. Anatomy of vestibular end organs and neural pathways. In: Cummings CW, Frederickson JM, Harker LA, et al., eds. *Otolaryngology—Head and Neck Surgery*. 3rd ed. St. Louis: Mosby, 1998:2561-2583.
9. Schuknecht HF. Pathophysiology. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:77-113.
10. Schuknecht HF. Developmental defects. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:115-189.
11. Nager GT. Dysplasia of the external and middle ear. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1993:83-118.
12. Nager GT. Dysplasia of the osseous and membranous cochlea and vestibular labyrinth. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1993:119-146.
13. Brownstein MH, Wanger N, Helwig EB. Accessory tragi. *Arch Dermatol* 1971; 104:625-631.
14. Olsen KD, Maragos NE, Weiland LH. First branchial cleft anomalies. *Laryngoscope* 1980; 90:423-436.
15. Work WP. Newer concepts of first branchial cleft defects. *Laryngoscope* 1972; 81:1581-1593.
16. Aronsohn RS, Bataskis JG, Rice DH, et al. Anomalies of the first branchial cleft. *Arch Otolaryngol* 1976; 102:737-740.
17. Lim LH, Hartnick CJ, Willging JP. A rare case of combined type I and II first branchial sinus. *J Pediatr Surg* 2003; 38:E12-E13.
18. Greenway RE, Hurst L, Fenton NA. An unusual first branchial cleft cyst. *J Otolaryngol* 1981; 10:219-225.
19. Schroeder JW Jr, Mohyuddin N, Maddalozzo J. Branchial anomalies in the pediatric population. *Otolaryngol Head Neck Surg* 2007; 137:289-295.
20. Triglia JM, Nicollas R, Ducroz V, et al. First branchial cleft anomalies: a study of 39 cases and a review of the literature. *Arch Otolaryngol Head Neck Surg* 1998; 124:291-295.
21. D'Souza AR, Uppal HS, De R, et al. Updating concepts of first branchial defects: a literature review. *Int J Pediatr Otorhinolaryngol* 2002; 62:103-109.
22. Bottrill ID, Chawla OP, Ramsay AD. Salivary gland choristoma of the middle ear. *J Laryngol Otol* 1992; 106:630-632.
23. Cannon CR. Salivary gland choristoma of the middle ear. *Am J Otol* 1980; 1:250-251.
24. Kenneth KL, Gruskin P, Carberry JN. Salivary gland choristoma of the middle ear. *Arch Pathol Lab Med* 1982; 106:39-40.
25. Kartush JM, Graham MD. Salivary gland choristoma of the middle ear: a case report and review of the literature. *Laryngoscope* 1984; 94:228-230.
26. Gulya AJ, Gassock ME III, Pensak ML. Neural choristoma of the middle ear. *Otolaryngol Head Neck Surg* 1987; 97:52-56.
27. Wazen J, Silverstein H, McDaniel A, et al. Brain tissue heterotopia in the eighth cranial nerve. *Otolaryngol Head Neck Surg* 1987; 96:373-378.
28. Glasscock ME III, Dickins JRE, Jackson CR, et al. Surgical management of brain tissue herniation into the middle ear and mastoid. *Laryngoscope* 1979; 89:1743-1754.
29. Moore PJ, Benjamin BNP, Kan AE. Salivary gland choristoma of the middle ear. *Int J Pediatr Otorhinolaryngol* 1984; 8:91-95.
30. Saeed YM, Bassis ML. Mixed tumor of the middle ear. A case report. *Arch Otolaryngol* 1971; 93:433-434.
31. Nager GT. Necrotizing ("malignant") granulomatous external otitis and osteomyelitis. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1993:192-206.
32. Weinroth SE, Schessel D, Tuazon CU. Malignant otitis externa in AIDS patients: case report and review of the literature. *Ear Nose Throat J* 1994; 73:772-774.
33. Shpitzer T, Stern Y, Cohen O, et al. Malignant external otitis in nondiabetic patients. *Ann Otol Rhinol Laryngol* 1993; 102:870-872.
34. Bernheim J, Sade J. Histopathology of the soft parts in 50 patients with malignant external otitis. *J Laryngol Otol* 1989; 103:366-368.
35. Al-Shihabi BA. Carcinoma of the temporal bone presenting as malignant otitis externa. *J Laryngol Otol* 1992; 106:908-910.
36. Grandis JR, Hirsch BE, Yu VL. Simultaneous presentation of malignant external otitis and temporal bone cancer. *Arch Otolaryngol Head Neck Surg* 1993; 119:687-689.
37. Chandler JR. Pathogenesis and treatment of facial paralysis due to malignant otitis externa. *Ann Otol Rhinol Laryngol* 1972; 81:1-11.
38. Damiani JM, Damiani KK, Kinney SE. Malignant external otitis with multiple cranial nerve involvement. *Am J Otol* 1979; 1:115-120.
39. Nager GT. Acute and chronic otitis media (tympanomastoiditis) and their regional and endocranial complications. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1993:220-297.
40. Goycoolea MV, Hueb MM, Ruah C. Definitions and terminology. *Otolaryngol Clin North Am* 1991; 24:757-761.
41. Wenig BM. Otitis media. In: Wenig BM, ed. *Atlas of Head and Neck Pathology*. 2nd ed. Edinburgh: Saunders Elsevier, 2008:740-745.
42. Barnes EL, Peel RL. Tympanosclerosis. In: Barnes L, ed. *Diseases of the External Auditory Canal, Middle Ear, and Temporal Bone*. 2nd ed. New York: Marcel Dekker, 2001:557-599.
43. Bhaya MH, Scachern PA, Morizono T, et al. Pathogenesis of tympanosclerosis. *Otolaryngol Head Neck Surg* 1993; 109:413-420.
44. Gibb AG, Pang YT. Current considerations in the etiology and diagnosis of tympanosclerosis. *Eur Arch Otorhinolaryngol* 1994; 251:439-451.
45. Nager GT, Vanderveen TS. Cholesterol granuloma involving the temporal bone. *Ann Otol Rhinol Laryngol* 1976; 85:204-209.
46. Nager GT. Cholesterol granulomas. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1994:914-939.
47. Thedinger BA, Nadol JB Jr., Montgomery WW, et al. Radiographic diagnosis, surgical treatment, and long-term follow-up of cholesterol granulomas of the petrous apex. *Laryngoscope* 1989; 99:896-907.
48. Windle-Taylor PC, Bailey CM. Tuberculous otitis media: a series of 22 patients. *Laryngoscope* 1980; 90:1039-1044.
49. McNulty JS, Fassett RL. Syphilis: an otolaryngologic perspective. *Laryngoscope* 1981; 91:889-905.
50. McGill TJI. Mycotic infections of the temporal bone. *Arch Otolaryngol* 1978; 104:140-144.

51. Leek JH. Actinomycosis of the tympanomastoid. *Laryngoscope* 1974; 84:290-301.
52. Sandler ED, Sandler JM, Leboit P, et al. Pneumocystis carinii otitis media in AIDS: a case report and review of the literature regarding extrapulmonary pneumocystosis. *Otolaryngol Head Neck Surg* 1990; 103:817-821.
53. Schuknecht HF. Infections. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:191-253.
54. Wilson WR. The relationship of herpesvirus family to sudden hearing loss: a prospective clinical study and literature review. *Laryngoscope* 1986; 96:870-877.
55. Hyams VJ, Batsakis JG, Michaels L. Inflammatory polyps of the middle ear. In: Hartmann WH, Sobin LH, eds. *Tumors of the Upper Respiratory Tract and Ear*. Atlas of Tumor Pathology, Fascicle 25, 2nd Series. Washington, DC: Armed Forces Institute of Pathology, 1988:301.
56. Gaafar H, Maher A, Al-Ghazzawi E. Aural polypi: a histopathological and histochemical study. *ORL J Otorhinolaryngol Relat Spec* 1982; 44:108-115.
57. Wenig BM. Otitis media. In: Wenig BM, ed. *Atlas of head and neck pathology*. 2nd ed. Edinburgh: Saunders Elsevier, 2008:745-746.
58. Marks PV, Brookes GB. Myelomatosis presenting as an isolated lesion in the mastoid. *Laryngoscope* 1985; 99:903-906.
59. Azadeh B, Ardehali S. Malakoplakia of middle ear: a case report. *Histopathology* 1983; 7:129-134.
60. Azadeh B, Dabiri S, Moshfegh I. Malakoplakia of the middle ear. *Histopathology* 1991; 19:276-278.
61. Metzger SA, Goodman ML. Chondrodermatitis helices: a clinical re-evaluation and pathological review. *Laryngoscope* 1976; 86:1402-1412.
62. Shuman R, Helwig EB. Chondrodermatitis helices. *Am J Clin Pathol* 1954; 24:126-144.
63. Winkler M. Knotchenformige Erkrankung am helix (Chondrodermatitis nodularis chronica helices). *Arch Dermatol Syphilol* 1915; 212:278-285.
64. Goette DK. Chondrodermatitis nodularis chronica helices: a perforating necrobiotic granuloma. *J Am Acad Dermatol* 1980; 2:148-154.
65. Kitchens GG. Auricular wedge resection and reconstruction. *Ear Nose Throat J* 1989; 68:673-683.
66. Lawrence CM. The treatment of chondrodermatitis nodularis with cartilage removal alone. *Arch Dermatol* 1991; 127:530-535.
67. Hansen JE. Pseudocysts of the auricle in Caucasians. *Arch Otolaryngol Head Neck Surg* 1967; 85:13-14.
68. Heffner DK, Hyams VJ. Cystic chondromalacia (endochondral pseudocyst) of the auricle. *Arch Pathol Lab Med* 1986; 110:740-743.
69. Lazar RH, Heffner DK, Huges GB, et al. Pseudocyst of the auricle: a review of 21 cases. *Otolaryngol Head Neck Surg* 1986; 94:360-361.
70. Kontis TC, Goldstone A, Brown M, et al. Pathological quiz: auricular pseudocyst. *Arch Otolaryngol Head Neck Surg* 1992; 118:1128-1130.
71. Engel D. Pseudocysts of the auricle in Chinese. *Arch Otolaryngol* 1966; 83:197-202.
72. Borroni G, Brazzelli V, Merlino M. Pseudocyst of the auricle. A birthday ear pull. *Br J Dermatol* 1991; 125:292-294.
73. Glamb R, Kim R. Pseudocyst of the auricle. *J Am Acad Dermatol* 1984; 11:58-63.
74. Grabski WJ, Salasche SJ, McCollough ML, et al. Pseudocyst of the auricle associated with trauma. *Arch Dermatol* 1989; 125:528-530.
75. Choi S, Lam KH, Chan KW, et al. Endochondral pseudocyst of the auricle in Chinese. *Arch Otolaryngol* 1984; 110:792-796.
76. Ophir D, Marshak G. Needle aspiration and pressure sutures for auricular pseudocyst. *Plast Reconstr Surg* 1991; 87:783-784.
77. Shuknecht H. Exostoses of the external auditory canal. In: Shuknecht H, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:398-399.
78. Whitaker SR, Cordier A, Kosjakov S, et al. Treatment of external auditory canal exostoses. *Laryngoscope* 1998; 108:195-199.
79. Fisher EW, McManus TC. Surgery for external auditory canal exostoses and osteomata. *J Laryngol Otol* 1994; 108:106-110.
80. Graham MD. Osteomas and exostoses of the external auditory canal. A clinical, histopathological, and scanning electron microscopic study. *Ann Otol* 1979; 88:566-572.
81. Nager GT. Osteomas and exostoses. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1993:483-493.
82. Fenton JE, Turner J, Fagan PA. A histopathologic review of temporal bone exostoses and osteomata. *Laryngoscope* 1996; 106:624-628.
83. Villacin AB, Brigham LN, Bullough PG. Primary and secondary synovial chondrometaplasia: histopathologic and clinicoradiologic differences. *Hum Pathol* 1979; 10:439-451.
84. Allias-Montmayeur F, Durroux R, Dodart L, et al. Tumours and pseudotumorous lesions of the temporomandibular joint: a diagnostic challenge. *J Laryngol Otol* 1997; 111:776-781.
85. Nussenbaum B, Roland PS, Gilcrease MZ, et al. Extra-articular synovial chondromatosis of the temporomandibular joint: pitfalls in diagnosis. *Arch Otolaryngol Head Neck Surg* 1999; 125:1394-1397.
86. Psimopoulou M, Karakasis D, Magoudi D, et al. Synovial chondromatosis of the temporomandibular joint. *Br J Oral Maxillofac Surg* 1998; 36:317-318.
87. Wu CW, Chen YK, Lin LM, et al. Primary synovial chondromatosis of the temporomandibular joint. *J Otolaryngol* 2004; 33:114-119.
88. Deahl ST, Ruprecht A. Asymptomatic radiographically detected chondrometaplasia in the temporomandibular joint. *Oral Surg Oral Med Oral Pathol* 1991; 72:371-374.
89. Yu Q, Yang J, Wang P, et al. CT features of synovial chondromatosis in the temporomandibular joint. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; 97:524-528.
90. Sciot R, Dal Cin P, Bellemans J, et al. Synovial chondromatosis: clonal chromosome changes provide further evidence for a neoplastic disorder. *Virchows Arch* 1998; 433:189-191.
91. Karlis V, Glickman RS, Zaslow M. Synovial chondromatosis of the temporomandibular joint with intracranial extension. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86:664-666.
92. Bell G, Sharp CW, Fourie LR, et al. Conservative surgical management of synovial chondromatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84:592-593.
93. Davis RI, Hamilton A, Biggart JD. Primary synovial chondromatosis: a clinicopathologic review and assessment of malignant potential. *Hum Pathol* 1998; 29:683-688.
94. Ichikawa T, Miyauchi M, Nikai H, et al. Synovial chondrosarcoma arising in the temporomandibular joint. *J Oral Maxillofac Surg* 1998; 56:890-894.
95. Davis RI, Foster H, Arthur K, et al. Cell proliferation studies in primary synovial chondromatosis. *J Pathol* 1998; 184:18-23.
96. Ferlito A, Devaney KO, Rinaldo A, et al. Ear cholesteatoma versus cholesterol granuloma. *Ann Otol Rhinol Laryngol* 1997; 106:79-85.

97. Michaels L. Pathology of cholesteatomas: a review. *J R Soc Med* 1979; 72:366–369.
98. Schuknecht HF. Cholesteatoma. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:204–206.
99. Michaels L. An epidermoid formation in the developing middle ear: possible source of cholesteatoma. *J Laryngol Otol* 1986; 15:169–174.
100. Abramson M, Moriyama H, Huang CC. Histology, pathogenesis, and treatment of cholesteatoma. *Ann Otol Rhinol Laryngol Suppl* 1984; 112:125–128.
101. Sudhoff H, Tos M. Pathogenesis of attic cholesteatoma: clinical and immunohistochemical support for combination of retraction theory and proliferation theory. *Am J Otol* 2000; 21:786–792.
102. Kazahaya K, Potsic WP. Congenital cholesteatoma. *Curr Opin Otolaryngol Head Neck Surg* 2004; 12:398–403.
103. Persaud R, Hajioff D, Trinidad A, et al. Evidence-based review of aetiopathogenic theories of congenital and acquired cholesteatoma. *J Laryngol Otol* 2007; 121:1013–1019.
104. Abramson M, Huang CC. Localization of collagenase in human middle ear cholesteatoma. *Laryngoscope* 1977; 87:771–791.
105. Piepergerdes MC, Kramer BM, Behnke EE. Keratosis obturans and external auditory canal cholesteatoma. *Laryngoscope* 1980; 90:383–391.
106. Desloge RB, Carew JF, Finstad CL, et al. DNA analysis of human cholesteatomas. *Am J Otol* 1997; 18:155–159.
107. Tokuriki M, Noda I, Saito T, et al. Gene expression analysis of human middle ear cholesteatoma using complementary DNA arrays. *Laryngoscope* 2003; 113:808–814.
108. Yamamoto-Fukuda T, Aoki D, Hishikawa Y, et al. Possible involvement of keratinocyte growth factor and its receptor in enhanced epithelial-cell proliferation and acquired recurrence of middle-ear cholesteatoma. *Lab Invest* 2003; 83:123–136.
109. Sudhoff H, Dazert S, Gonzales AM, et al. Angiogenesis and angiogenic growth factors in middle ear cholesteatoma. *Am J Otol* 2000; 21:793–798.
110. Vikram BK, Udayashankar SG, Naseeruddin K, et al. Complications in primary and secondary acquired cholesteatoma: a prospective comparative study of 62 ears. *Am J Otolaryngol* 2008; 29:1–6.
111. Smith JA, Danner CJ. Complications of chronic otitis media and cholesteatoma. *Otolaryngol Clin North Am* 2006; 39:1237–1255.
112. Bennett M, Warren F, Jackson GC, et al. Congenital cholesteatoma: theories, facts, and 53 patients. *Otolaryngol Clin North Am* 2006; 39:1081–1094.
113. Lazard DS, Roger G, Denoyelle F, et al. Congenital cholesteatoma: risk factors for residual disease and retraction pockets—a report on 117 cases. *Laryngoscope* 2007; 117:634–637.
114. Willman CL. Detection of clonal histiocytes in Langerhans cell histiocytosis: biology and clinical significance. *Br J Cancer Suppl* 1994; 23:S29–S33.
115. Willman CL, Busque L, Griffith BB, et al. Langerhans'—cell histiocytosis (histiocytosis X)—a clonal proliferative disease. *N Engl J Med* 1994; 331:154–160.
116. Lieberman PH, Jones CR, Steinman RM, et al. Langerhans cell (eosinophilic) granulomatosis: a clinicopathologic study encompassing 50 years. *Am J Surg Pathol* 1997; 20:519–552.
117. Appling D, Jenkins HA, Parton GA. Eosinophilic granuloma in the temporal bone and skull. *Otolaryngol Head Neck Surg* 1983; 91:358–365.
118. al-Amman AY, Tewfik TL, Bond M, et al. Langerhans' cell histiocytosis: paediatric head and neck study. *J Otolaryngol* 1999; 28:266–272.
119. Cochrane LA, Prince M, Clarke K. Langerhans' cell histiocytosis in the paediatric population: presentation and treatment of head and neck manifestations. *J Otolaryngol* 2003; 32:33–37.
120. Saliba I, El Fata F, Arcand P, et al. Langerhans' cell histiocytosis of the temporal bone in children. *Int J Pediatr Otorhinolaryngol* 2008; 72(6):775–786.
121. Azumi N, Sheibani K, Swartz WG, et al. Antigenic phenotype of Langerhans cell histiocytosis: an immunohistochemical study demonstrating the value of LN-2, LN-3 and vimentin. *Hum Pathol* 1988; 19:1376–1382.
122. Beckstead JH, Wood GS, Turner RR. Histiocytosis X cells and Langerhans cells: enzyme histochemical and immunologic similarities. *Hum Pathol* 1984; 15:826–833.
123. Emile JF, Wechsler J, Brousse N, et al. Langerhans' cell histiocytosis. Definitive diagnosis with the use of monoclonal antibody O10 on routinely paraffin-embedded samples. *Am J Surg Pathol* 1995; 19:636–641.
124. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. *Am J Surg Pathol* 2008; 32:615–619.
125. Ide F, Iwase T, Saito I, et al. Immunohistochemical and ultrastructural analysis of the proliferating cells in histiocytosis X. *Cancer* 1984; 53:917–921.
126. Wenig BM, Abbondanzo SL, Childers E, et al. Extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) of the head and neck. *Hum Pathol* 1993; 24:483–492.
127. Ramalingam KK, Ramalingam R, Sreenivasamurthy TM, et al. Management of temporal bone meningoencephalocoele. *J Laryngol Otol* 2008; 17:1–7.
128. Sdano MT, Pensak ML. Temporal bone encephaloceles. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13:287–289.
129. Johnson F, Semaan MT, Megerian CA. Temporal bone fracture: evaluation and management in the modern era. *Otolaryngol Clin North Am* 2008; 41:597–618.
130. Jaksch-Wartenhorst R. Polychondropathia. *Wien Arch Intern Med* 1923; 6:93–100.
131. Damiani JM, Levine HL. Relapsing polychondritis—report of ten cases. *Laryngoscope* 1979; 89:929–946.
132. McAdam LP, O'Hanlan MA, Bluestone R, et al. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. *Medicine* 1976; 55:193–215.
133. Cody DT, Sones DA. Relapsing polychondritis: audiovestibular manifestations. *Laryngoscope* 1971; 81:1208–1222.
134. McCaffrey TV, McDonald TJ, McCaffrey LA. Head and neck manifestations of relapsing polychondritis: review of 29 cases. *Otolaryngol* 1978; 86:473–478.
135. Letko E, Zafirakis P, Baltatzis S, et al. Relapsing polychondritis: a clinical review. *Semin Arthritis Rheum* 2002; 31:384–395.
136. Rapini RP, Warner NB. Relapsing polychondritis. *Clin Dermatol* 2006; 24:482–485.
137. Bachor E, Blevins NH, Karmody C, et al. Otolologic manifestations of relapsing polychondritis. Review of literature and report of nine cases. *Auris Nasus Larynx* 2006; 33:135–141.
138. Tesche S, Wenzel S, Sagowski C. Relapsing polychondritis—a case report and review of the literature. *Laryngorhinootologie* 2005; 84:352–356.
139. Ogawa H, Nishi E, Kameda H, et al. Manifestations mimicking relapsing polychondritis in a patient with microscopic polyangiitis. *Nihon Rinsho Meneki Gakkai Kaishi* 2005; 28:104–108.
140. Tsuda T, Nakajima A, Baba S, et al. A case of relapsing polychondritis with bilateral sensorineural hearing loss and perforation of the nasal septum at the onset. *Mod Rheumatol* 2007; 17:148–152.

141. Schumacher HR Jr. Relapsing polychondritis. In: Goldman L, Bennett JC, eds. *Cecil Textbook of Medicine*. 21st ed. Philadelphia: WB Saunders, 2000:1550.
142. Harisdangkul V, Johnson WW. Association between relapsing polychondritis and systemic lupus erythematosus. *South Med J* 1994; 87:753-757.
143. Dolan DL, Lemmon GB Jr., Teitelbaum SL. Relapsing polychondritis: analytical literature review and studies on pathogenesis. *Am J Med* 1966; 41:285-299.
144. Ebringer B, Rook G, Swana T, et al. Autoantibodies to cartilage and type II collagen in relapsing polychondritis and other rheumatic diseases. *Ann Rheum Dis* 1981; 40:473-479.
145. Valenzuela R, Cooperrider PA, Gogate P, et al. Relapsing polychondritis: immunomicroscopic findings in cartilage of ear biopsy specimens. *Hum Pathol* 1980; 11:19-22.
146. Helm TN, Valenzuela R, Glanz S, et al. Relapsing polychondritis: a case diagnosed by direct immunofluorescence and coexisting with pseudocyst of the auricle. *J Am Acad Dermatol* 1992; 26:315-318.
147. Irani BS, Martin-Hirsch DP, Clark D, et al. Relapsing polychondritis—a study of four cases. *J Laryngol Otol* 1992; 106:911-914.
148. Lang B, Rothenfusser A, Lanchbury JS, et al. Susceptibility to relapsing polychondritis is associated with HLA-DR4. *Arthritis Rheum* 1993; 36:660-664.
149. Grahame R, Scott JT. Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970; 29:461-468.
150. Resnick D, Nikiyama G. Gouty arthritis. In: Resnick D, Niwayama G, eds. *Diagnosis of Bone and Joint Disorders*. 2nd ed. Philadelphia: WB Saunders, 1988:1618-1671.
151. McCarty DJ, Hollander JL. Identification of urate crystals in gouty synovial fluid. *Ann Intern Med* 1961; 54:452-460.
152. Ishida T, Dorfman HD, Bullough PG. Tophaceous pseudogout (tumoral calcium pyrophosphate dihydrate crystal deposition disease). *Hum Pathol* 1995; 26:587-593.
153. Vargas A, Teruel J, Trull J, et al. Calcium pyrophosphate dihydrate crystal deposition disease presenting as a pseudotumor of the temporomandibular joint. *Eur Radiol* 1997; 7:1452-1453.
154. Illum P, Thorling K. Otologic manifestations of Wegener's granulomatosis. *Laryngoscope* 1982; 92:801-804.
155. Kornblut AD, Wolff SM, Fauci AS. Ear disease in patients with Wegener's granulomatosis. *Laryngoscope* 1982; 92:713-717.
156. McCaffrey TV, McDonald TJ, Facer GW, et al. Otologic manifestations of Wegener's granulomatosis. *Otolaryngol Head Neck Surg* 1980; 88:586-593.
157. Takagi D, Nakamura Y, Maguschi S, et al. Otologic manifestations of Wegener's granulomatosis. *Laryngoscope* 2002; 112:1684-1690.
158. Okamura H, Ohtani I, Anzai T. The hearing loss in Wegener's granulomatosis: relationship between hearing loss and serum ANCA. *Auris Nasus Larynx* 1992; 19:1-6.
159. Fauci AS, Haynes BF, Katz P, et al. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98:76-85.
160. Nolle B, Specks U, Ludemann J, et al. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener's granulomatosis. *Ann Intern Med* 1989; 111:28-40.
161. DeRemee RA. Antineutrophil cytoplasmic autoantibody-associated diseases: a pulmonologist's perspective. *Am J Kidney Dis* 1991; 18:180-183.
162. Specks U, Wheatley CL, McDonald TJ, et al. Anticytoplasmic autoantibodies in the diagnosis and follow-up of Wegener's granulomatosis. *Mayo Clin Proc* 1989; 64:28-36.
163. Braun MG, Csernok E, Gross WL, et al. Proteinase 3, the target antigen of anticytoplasmic antibodies circulating in Wegener's granulomatosis. Immunolocalization in normal and pathologic tissues. *Am J Pathol* 1991; 139:831-838.
164. Csernok E, Holle J, Hellmich B, et al. Evaluation of capture ELISA for detection of antineutrophil cytoplasmic antibodies directed against proteinase 3 in Wegener's granulomatosis: first results from a multicentre study. *Rheumatology (Oxford)* 2004; 43:174-180.
165. McDonald TJ, Remee RA. Wegener's granulomatosis. *Laryngoscope* 1983; 93:220-231.
166. Wolf M, Kronenberg J, Engelberg S, et al. Rapidly progressive hearing loss as a symptom of polyarteritis nodosa. *Am J Otolaryngol* 1987; 8:105-108.
167. Gussen R. Atypical ossicle joint lesions in rheumatoid arthritis with sicca syndrome (Sjögren's syndrome). *Arch Otolaryngol* 1977; 103:284-286.
168. House JW. Otosclerosis. In: Cummings CW, Frederickson JM, Harker LA, et al., eds. *Otolaryngology—Head and Neck Surgery*. 3rd ed. St. Louis: Mosby, 1998:3126-3135.
169. Cody DT, Baker HL Jr. Otosclerosis: vestibular symptoms and sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1978; 87:778-796.
170. Morales-Garcia C. Cochleo-vestibular involvement in otosclerosis. *Acta Otolaryngol* 1972; 73:484-492.
171. Schuknecht HF. Otosclerosis. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:365-379.
172. Vicente Ade O, Yamasita HK, Albernaz PL, et al. Computed tomography in the diagnosis of otosclerosis. *Otolaryngol Head Neck Surg* 2006; 134:685-692.
173. Lescanne E, Bakhos D, Metais JP, et al. Otosclerosis in children and adolescents: a clinical and CT-scan survey with review of the literature. *Int J Pediatr Otorhinolaryngol* 2008; 72:147-152.
174. Moumoulidis I, Axon P, Baguley D, et al. A review on the genetics of otosclerosis. *Clin Otolaryngol* 2007; 32:239-247.
175. Schuknecht HF. Paget's disease. In: Schuknecht HF, ed. *Pathology of the Ear*. 2nd ed. Philadelphia: Lea & Febiger, 1993:379-390.
176. Davies DG. Paget's disease of the temporal bone. A clinical and histopathological survey. *Acta Otolaryngol* 1968; (suppl 242):7-47.
177. D'Archambeau O, Parizel PM, Koelkelkoren E, et al. CT diagnosis and differential diagnosis of otodystrophic lesions of the temporal bone. *Eur J Radiol* 1990; 11:22-30.
178. Haibach H, Farrell C, Dittrich FJ. Neoplasms arising in Paget's disease of bone: a study of 82 cases. *Am J Clin Pathol* 1985; 83:594-600.
179. Wick MR, McLeod RA, Siegel GP, et al. Sarcomas of bone arising complicating osteitis deformans (Paget's disease). Fifty years' experience. *Am J Surg Pathol* 1981; 5:47-59.
180. Nager GT. Meniere's disease. In: Nager GT, ed. *Pathology of the Ear and Temporal Bone*. Baltimore: Williams & Wilkins, 1994:1213-1228.
181. Morrison AW, Mowbray JF, Williamson R, et al. On genetic and environmental factors in Meniere's disease. *Am J Otol* 1994; 15:35-39.
182. Ruckenstein MJ, Rutka JA, Hawke M. The treatment of Meniere's disease: torok revisited. *Laryngoscope* 1991; 101:211-218.
183. Xenellis J, Morrison AW, McClowskey D, et al. HLA antigen in the pathogenesis of Meniere's disease. *J Laryngol Otol* 1986; 100:21-24.
184. Birgerson L, Gustavson K, Stahle J. Familial Meniere's disease: a genetic investigation. *Am J Otol* 1987; 8:823-826.
185. Paparella MM. The cause (multifactorial inheritance) and pathogenesis (endolymphatic malabsorption) of Meniere's disease and its symptoms (mechanical and chemical). *Acta Otolaryngol* 1985; 99:445-451.

186. Klis SFL, Buijs J, Smoorenburg GF. Quantification of the relationship between electrophysiologic and morphologic changes in experimental endolymphatic hydrops. *Ann Otol Rhinol Laryngol* 1990; 99:566-570.
187. Schessel DA, Minor LB, Nedzelski J. Meniere's disease and other peripheral vestibular disorders. In: Cummings CW, Frederickson JM, Harker LA, et al., eds. *Otolaryngology—Head and Neck Surgery*. 3rd ed. St. Louis: Mosby, 1998:2672-2705.
188. Torok N. Old and new in Meniere's disease. *Laryngoscope* 1977; 87:1870-1877.
189. Hyams VJ, Batsakis JG, Michaels L. Adenomatous neoplasms of ceruminous gland origin. In: Hartmann W, Sobin LS, eds. *Tumors of the Upper Respiratory Tract and Ear. Atlas of Tumor Pathology, Fascicle 25, 2nd Series*. Washington, DC: Armed Forces Institute of Pathology, 1988:285-291.
190. Wetli CV, Prado V, Millard M, et al. Tumors of ceruminous glands. *Cancer* 1972; 29:1169-1178.
191. Pulec JL. Glandular tumors of the external auditory canal. *Laryngoscope* 1977; 87:1601-1612.
192. Wolf BA, Gluckman JL, Wirman JA. Benign dermal cylindroma of the external auditory canal: a clinicopathologic report. *Am J Otolaryngol* 1985; 6:35-38.
193. Thompson LD, Nelson BL, Barnes EL. Ceruminous adenomas: a clinicopathologic study of 41 cases with a review of the literature. *Am J Surg Pathol* 2004; 28:308-318.
194. Schenk P, Handisurya A, Steurer M. Ultrastructural morphology of a middle ear ceruminoma. *ORL J Otorhinolaryngol Relat Spec* 2002; 64:358-363.
195. Tran LP, Grunfast KM, Selesnick SH. Benign lesions of the external auditory canal. *Otolaryngol Clin North Am* 1996; 29:807-825.
196. Johnson IJ, Tadpatrikar MH, Sharp JF. Chondroma of the external auditory canal. *J Laryngol Otol* 1998; 112:278-279.
197. Petschenik AJ, Linstrom CJ, McCormick SA. Leiomyoma of the external auditory canal. *Am J Otol* 1996; 17:133-136.
198. Lewis WB, Mattucci KF, Smilari T. Schwannoma of the external auditory canal: an unusual finding. *Int Surg* 1995; 80:287-290.
199. Ferreiro JA, Carney JA. Myxomas of the external ear and their significance. *Am J Surg Pathol* 1994; 18:274-280.
200. Hyams VJ, Batsakis JG, Michaels L. Neoplasms of the middle ear. In: Hartmann W, Sobin LS, eds. *Tumors of the Upper Respiratory Tract and Ear. Atlas of Tumor Pathology, Fascicle 25, 2nd Series*. Washington, DC: Armed Forces Institute of Pathology, 1986:306-330.
201. Mills SE, Frierson H Jr., Gaffney M. Neoplasms of the middle ear. In: Rosai J, Sobin LS, eds. *Tumors of the Upper Respiratory Tract and Ear. Atlas of Tumor Pathology, Fascicle 25, 2nd Series*. Washington, DC: Armed Forces Institute of Pathology, 2001:383-450.
202. Wenig BM. Immunohistochemistry of middle ear neoplasms. In: Wenig BM, ed. *Atlas of head and neck pathology*. 2nd ed. Edinburgh: Saunders Elsevier, 2008:812.
203. Torske KR, Thompson LD. Adenoma versus carcinoid tumor of the middle ear: a study of 48 cases and review of the literature. *Mod Pathol* 2002; 15:543-555.
204. Stanley MW, Horwitz CA, Levinson RM, et al. Carcinoid tumors of the middle ear. *Am J Clin Pathol* 1987; 87:592-600.
205. Latif MA, Madders DJ, Shaw PA. Carcinoid tumour of the middle ear associated with systemic symptoms. *J Laryngol Otol* 1987; 101:480-486.
206. Manni J, Faverly DR, van Haelst UJ. Primary carcinoid tumor of the middle ear: report of four cases and a review of the literature. *Arch Otolaryngol Head Neck Surg* 1992; 118:1341-1347.
207. Faverly DR, Manni J, Smedts F et al. Adenocarcinoid or amphotericin tumors of the middle ear. *Pathol Res Pract* 1992; 188:162-171.
208. Batsakis JG. Adenomatous tumors of the middle ear. *Ann Otol Rhinol Laryngol* 1989; 98:749-752.
209. El-Naggar AK, Pflatz M, Ordóñez NG, et al. Tumors of the middle ear and endolymphatic sac. *Pathol Annu* 1994; 29:199-231.
210. Ramsey MJ, Nadol JB Jr., Pilch BZ, et al. Carcinoid tumor of the middle ear: clinical features, recurrences, and metastases. *Laryngoscope* 2005; 115:1660-1666.
211. Larson TC, Reese DF, Baker HL, et al. Glomus tympanicum chemodectomas: radiographic and clinical characteristics. *Radiology* 1987; 163:801-806.
212. Persky MS, Hu KS, Berenstein A. Paragangliomas of the head and neck. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer. A Multidisciplinary Approach*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2004:678-713.
213. Lemaire M, Persu A, Hainaut P, et al. Hereditary paraganglioma. *J Intern Med* 1999; 246:113-116.
214. Bikhazi PH, Messina L, Mhatre AN, et al. Molecular pathogenesis in sporadic head and neck paraganglioma. *Laryngoscope* 2000; 110:1346-1348.
215. Petropoulos AE, Luetje CM, Camarata PJ, et al. Genetic analysis in the diagnosis of familial paragangliomas. *Laryngoscope* 2000; 110:1225-1229.
216. Johnson TL, Zarbo RJ, Lloyd RV, et al. Paragangliomas of the head and neck: immunohistochemical neuroendocrine and intermediate filament typing. *Mod Pathol* 1998; 1:216-223.
217. Klierer KE, Wen DR, Cancilla PA, et al. Paragangliomas: assessment of prognosis by histologic, immunohistochemical, and ultrastructural techniques. *Hum Pathol* 1989; 20:29-39.
218. Hu K, Persky MS. Multidisciplinary management of paragangliomas of the head and neck, Part 1. *Oncology* 2003; 17:983-993.
219. Barnes L, Taylor SR. Carotid body paragangliomas. A clinicopathologic and DNA analysis of 13 cases. *Arch Otolaryngol Head Neck Surg* 1990; 116:447-453.
220. Spector GJ, Ciralsky RH, Ogura JH. Glomus tumors in the head and neck. III. Analysis of clinical manifestations. *Ann Otol Rhinol Laryngol* 1975; 84:73-79.
221. Taylor DM, Alford BR, Greenberg SD. Metastases of glomus jugulare tumors. *Arch Otolaryngol* 1965; 82:5-13.
222. Johnstone PA, Foss RD, Desilets DJ. Malignant jugulotympanic paraganglioma. *Arch Pathol Lab Med* 1990; 114:976-979.
223. Erickson LS, Sorenson GD, McGavran MH. A review of 140 acoustic neurinomas (neurilemmoma). *Laryngoscope* 1965; 75:601-627.
224. Kasantikul V, Netsky MG, Glasscock ME III, et al. Acoustic neurilemmoma. Clinicoanatomical study of 103 patients. *J Neurosurg* 1980; 52:28-35.
225. Martuza RL, Ojemann RG. Bilateral acoustic neuromas: clinical aspects, pathogenesis and treatment. *Neurosurgery* 1982; 10:1-12.
226. Anand T, Byrnes DP, Walby AP, et al. Bilateral acoustic neuromas. *Clin Otolaryngol* 1993; 18:365-371.
227. Moffat DA, Irving RM. The molecular genetics of vestibular schwannomas. *J Laryngol Otol* 1995; 109:381-384.
228. Kishore A, O'Reilly BF. A clinical study of vestibular schwannomas in type 2 neurofibromatosis. *Clin Otolaryngol* 2000; 25:561-565.
229. Thompson LD, Bouffard JP, Sandberg GD, et al. Primary ear and temporal bone meningiomas: a clinicopathologic study of 36 cases with a review of the literature. *Mod Pathol* 2003; 16:236-245.

230. Simon M, Boström JP, Hartman C. Molecular genetics of meningiomas: from basic research to potential clinical applications. *Neurosurgery* 2007; 60:787–798.
231. Rietz DR, Ford CN, Kurtycz DF, et al. Significance of apparent intratympanic meningiomas. *Laryngoscope* 1983; 93:1397–1404.
232. Wenig BM. Schneiderian papillomas of the middle ear. *Ann Otol Rhinol Laryngol* 1996; 105:226–233.
233. Andrade JM, Gehris CW Jr, Breitnecker R. Cavernous haemangioma of the tympanic membrane. A case report. *Am J Otol* 1993; 4:198–199.
234. Jackson CG, Levine SC, McKenna KX. Hemangioma of the middle ear. *Am J Otol* 1987; 8:131–132.
235. Eby TL, Fisch U, Malek MS. Facial nerve management in temporal bone hemangiomas. *Am J Otol* 1992; 13: 223–232.
236. Olson JE, Glasscock ME III, Britton BH. Lipomas of the internal auditory canal. *Arch Otolaryngol* 1978; 104:431–436.
237. Huang TS. Primary intravestibular lipoma. *Ann Otol Rhinol Laryngol* 1989; 98:393–395.
238. Ishikawa T, Saito H, Takahashi K. Osteoma of the mastoid. *Arch Otorhinolaryngol* 1997; 217:93–97.
239. Denia A, Perez F, Canalis RR, et al. Extracanalicular osteomas of the temporal bone. *Arch Otolaryngol* 1979; 105:706–709.
240. Marlowe FI, Dave U, Wolfson RJ. Giant osteoma of the mastoid. *Am J Otolaryngol* 1980; 1:191–193.
241. Potter C, Conner GH, Sharkey FE. Benign osteoblastoma of the temporal bone. *Am J Otol* 1983; 4:318–322.
242. Bertoni F, Unni KK, Beabout JW, et al. Chondroblastoma of the skull and facial bones. *Am J Clin Pathol* 1987; 88: 1–9.
243. Silverstein H, Griffin WL Jr., Balough K Jr. Teratoma of the middle ear and mastoid process. A case with aberrant innervation of the facial musculature. *Arch Otolaryngol* 1967; 85:243–248.
244. Megerian CA, McKenna MJ, Nuss RC, et al. Endolymphatic sac tumors: histopathologic confirmation, clinical characterization, and implication in von Hippel-Lindau disease. *Laryngoscope* 1995; 105:801–808.
245. Manski TJ, Heffner DK, Glenn GM, et al. Endolymphatic sac tumors: the basis of morbid hearing loss in von Hippel-Lindau disease. *JAMA* 1997; 277:1461–1466.
246. Wenig BM, Heffner DK. Endolymphatic sac tumors: fact or fiction? *Adv Anat Pathol* 1996; 3:378–387.
247. Batsakis JG, El-Naggar AK. Papillary neoplasms (Heffner's tumors) of the endolymphatic sac. *Ann Otol Rhinol Laryngol* 1993; 102:648–651.
248. Heffner DK. Low-grade adenocarcinoma of probable endolymphatic sac origin. A clinicopathologic study of 20 cases. *Cancer* 1989; 64:2292–2302.
249. Sgambati MT, Stolle C, Choyke PL, et al. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. *Am J Hum Genet* 2000; 66:84–91.
250. Vandeweyer E, Thill MP, Deraemaeker R. Basal cell carcinoma of the external auditory canal. *Acta Chir Belg* 2002; 102:137–140.
251. Ahmad I, Das Gupta AR. Epidemiology of basal cell carcinoma and squamous cell carcinoma of the pinna. *J Laryngol Otol* 2001; 115:85–86.
252. Unden AB, Holmberg C, Lund-Rozell B, et al. Mutations in the human homologue of drosophila patched (PTCH) in basal cell carcinoma and the Gorlin syndrome: different in vivo mechanisms of PTCH inactivation. *Cancer Res* 1996; 56:4562–4565.
253. Manfredi M, Vescovi P, Bonanini M. Nevroid basal cell carcinoma syndrome: a review of the literature. *Int J Oral Maxillofac Surg* 2004; 33:117–124.
254. Boonen SE, Stahl D, Kreiborg S, et al. Delineation of an interstitial 9q22 deletion in basal cell nevus syndrome. *Am J Med Genet A* 2004; 132A:324–328.
255. Midro AT, Panasiuk B, Tumer Z, et al. Interstitial deletion 9q22.32-q33.2 associated with additional familial translocation t(9;17)(q34.11;p11.2) in a patient with Gorlin-Goltz syndrome and features of Nail-Patella syndrome. *Am J Med Genet A* 2004; 124:179–191.
256. Ting PT, Kaspar R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. *J Cutan Med Surg* 2005; 9:10–15.
257. Martin RC 2nd, Edwards MJ, Cawte TG, et al. Basosquamous carcinoma: analysis of prognostic factors influencing recurrence. *Cancer* 2000; 88:1365–1369.
258. Lehnerdt G, Manz D, Jahnke K, et al. Cutaneous basosquamous cell carcinoma. *HNO* 2008; 56:306–311.
259. Bowman PH, Ratz JL, Knoepf TG, et al. Basosquamous carcinoma. *Dermatol Surg* 2003; 29:830–832.
260. Byers R, Kesler K, Redmon B, et al. Squamous carcinoma of the external ear. *Am J Surg* 1983; 146:447–450.
261. Conley J, Schuller DE. Malignancies of the ear. *Laryngoscope* 1976; 86:1147–1163.
262. Johns ME, Headington JT. Squamous cell carcinoma of the external auditory canal. A clinicopathologic study of 20 cases. *Arch Otolaryngol Head Neck Surg* 1974; 100:45–49.
263. Yin M, Ishikawa K, Honda K. Analysis of 95 cases of squamous cell carcinoma of the external and middle ear. *Auris Nasus Larynx* 2006; 33:251–257.
264. Olsen KD, DeSanto LW, Forbes GS. Radiographic assessment of squamous cell carcinoma of the temporal bone. *Laryngoscope* 1983; 93:1162–1167.
265. Arriaga M, Curtin HD, Takahashi H, et al. The role of preoperative CT scans in staging external auditory meatus carcinoma: radiologic-pathologic correlation study. *Otolaryngol Head Neck Surg* 1991; 105:6–11.
266. Ogawa K, Nakamura K, Hatano K, et al. Treatment and prognosis of squamous cell carcinoma of the external auditory canal and middle ear: a multi-institutional retrospective review of 87 patients. *Int J Radiat Oncol Biol Phys* 2007; 68:1326–1334.
267. Arriaga M, Hirsch BE, Kamerer DB, et al. Squamous cell carcinoma of the external auditory meatus (canal). *Otolaryngol Head Neck Surg* 1989; 101:330–337.
268. Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. *J Am Acad Dermatol* 1992; 26:976–990.
269. Nakagawa T, Kumamoto Y, Natori Y, et al. Squamous cell carcinoma of the external auditory canal and middle ear: an operation combined with preoperative chemoradiotherapy and a free surgical margin. *Otol Neurotol* 2006; 27:242–248.
270. Choi JY, Choi EC, Lee HK, et al. Mode of parotid involvement in external auditory canal carcinoma. *J Laryngol Otol* 2003; 117:951–954.
271. Shockley WW, Stucker FJ Jr. Squamous cell carcinoma of the external ear: a review of 75 cases. *Otolaryngol Head Neck Surg* 1987; 97:308–312.
272. Thomas SS, Matthews RN. Squamous cell carcinoma of the pinna: a 6-year study. *Br J Plast Surg* 1994; 47:81–85.
273. Lee D, Nash M, Har-El G. Regional spread of auricular and periauricular cutaneous malignancies. *Laryngoscope* 1996; 106:998–1001.
274. Arriaga M, Curtin H, Takahashi H, et al. Staging proposal for external auditory meatus carcinoma based on preoperative clinical examination and computed tomographic findings. *Ann Otol Rhinol Laryngol* 1990; 99:714–721.
275. Moody SA, Hirsch BE, Myers EN. Squamous cell carcinoma of the external auditory canal: an evaluation of a staging system. *Am J Otol* 2000; 21:582–588.

276. Hicks GW. Tumors arising from the glandular structures of the external auditory canal. *Laryngoscope* 1983; 93:326–340.
277. Perzin KH, Gullane P, Conley J. Adenoid cystic carcinoma involving the external auditory canal. A clinicopathological study of 16 cases. *Cancer* 1982; 50:2873–2883.
278. Weiss SW, Goldblum JR. Malignant fibrohistiocytoma (pleomorphic undifferentiated sarcoma) In: Weiss SW, Goldblum JR, eds. *Enzinger and Weiss's Soft Tissue Tumors*. 5th ed. Philadelphia: Mosby Elsevier, 2008: 403–427.
279. Dei Tos AP, Maestro R, Doglioni C, et al. Ultraviolet induced p53 mutations in atypical fibroxanthoma. *Am J Pathol* 1994; 145:11–17.
280. Calonje E, Wadden C, Wilson-Jones E, et al. Spindle-cell non-pleomorphic atypical fibroxanthoma: analysis of a series and delineation of a distinctive variant. *Histopathol* 1993; 22:247–254.
281. Bruecks AK, Medlicott SA, Trotter MJ. Atypical fibroxanthoma with prominent sclerosis. *J Cutan Pathol* 2003; 30:336–339.
282. Crowson AN, Carlson-Sweet K, Macinnis C, et al. Clear cell atypical fibroxanthoma: a clinicopathologic study. *J Cutan Pathol* 2002; 29:374–381.
283. Orosz Z, Kelemen J, Szentirmay Z. Granular cell variant of atypical fibroxanthoma. *Pathol Oncol Res* 1996; 2:244–247.
284. Orlandi A, Bianchi L, Ferlosio A, et al. The origin of osteoclast-like giant cells in atypical fibroxanthoma. *Histopathology* 2003; 42:407–410.
285. Diaz-Cascajo C, Weyers W, Borghi S. Pigmented atypical fibroxanthoma: a tumor that may be easily mistaken for malignant melanoma. *Am J Dermatopathol* 2003; 25:1–5.
286. Ma CK, Zarbo RJ, Gown AM. Immunohistochemical characterization of atypical fibroxanthoma and dermatofibrosarcoma protuberans. *Am J Clin Pathol* 1992; 97: 478–483.
287. Longacre TA, Smoller BR, Rouse RV. Atypical fibroxanthoma. Multiple immunohistologic profiles. *Am J Surg Pathol* 1993; 17:1199–1209.
288. Monteagudo C, Calduch L, Navarro S, et al. CD99 immunoreactivity in atypical fibroxanthoma: a common feature of diagnostic value. *Am J Clin Pathol* 2002; 117:126–131.
289. Smith-Zagone MJ, Prieto VG, Hayes RA, et al. HMB-45 (gp103) and MART-1 expression within giant cells in an atypical fibroxanthoma: a case report. *J Cutan Pathol* 2004; 31:284–286.
290. Barr RJ, Wueker RB, Graham JH. Ultrastructure of atypical fibroxanthoma. *Cancer* 1977; 40:736–743.
291. Mihic-Probst D, Zhao J, Saremaslani P, et al. CGH analysis shows genetic similarities and differences in atypical fibroxanthoma and undifferentiated high grade pleomorphic sarcoma. *Anticancer Res* 2004; 24:19–26.
292. Sakamoto A, Oda Y, Itakura E, et al. H-, K-, and N-ras gene mutation in atypical fibroxanthoma and malignant fibrous histiocytoma. *Hum Pathol* 2001; 32:1225–1231.
293. Kenyon GS, Marks PV, Scholtz CL, et al. Squamous cell carcinoma of the middle ear. A 25-year retrospective study. *Ann Otol Rhinol Laryngol* 1985; 94:273–277.
294. Hyams VJ, Batsakis JG, Michaels L. Squamous cell carcinoma of the middle ear. In: Hartmann WH, Sobin LH, eds. *Tumors of the Upper Respiratory Tract and Ear. Atlas of Tumor Pathology, Fascicle 25, 2nd Series*. Washington, DC: Armed Forces Institute of Pathology, 1986:326–327.
295. Tsai ST, Li C, Jun YT, et al. High prevalence of human papillomavirus types 16 and 18 in middle ear carcinomas. *Int J Cancer* 1997; 71:208–212.
296. Moore MG, Deschler DG, McKenna MJ, et al. Management outcomes following lateral temporal bone resection for ear and temporal bone malignancies. *Otolaryngol Head Neck Surg* 2007; 137:893–898.
297. Pemberton LS, Swindell R, Sykes AJ. Primary radical radiotherapy for squamous cell carcinoma of the middle ear and external auditory canal—a historical series. *Clin Oncol (R Coll Radiol)* 2006; 18:390–394.
298. Hyams VJ, Batsakis JG, Michaels L. Adenocarcinoma of the middle ear. In: Hartmann, WH, Sobin LH, eds. *Tumors of the Upper Respiratory Tract and Ear. Atlas of Tumor Pathology, Fascicle 25, 2nd Series*. Washington, DC: Armed Forces Institute of Pathology, 1986:320–323.
299. Nora FE, Unni KK, Pritchard DJ. Osteosarcoma of extragnathic craniofacial bones. *Mayo Clin Proc* 1983; 58:268–272.
300. Huvos AG, Sandaresan N, Bretsky SS. Osteogenic sarcoma of the skull. A clinicopathologic study of 19 patients. *Cancer* 1985; 56:1214–1221.
301. Caron AS, Hajdu SI, Strong EW. Osteogenic sarcoma of the facial and cranial bones. A review of forty-three cases. *Am J Surg* 1971; 122:719–725.
302. Coltera MC, Googe PB, Harriest TJ, et al. Chondrosarcoma of the temporal bone. Diagnosis and treatment in 13 cases and review of the literature. *Cancer* 1986; 58:2689–2696.
303. Schuknecht HF. Neoplastic growths. In: Schuknecht HF, ed. *Pathology of the Ear*. Philadelphia: Lea & Febiger, 1993:447–498.
304. Davis GL. Secondary tumours. In: Barnes L, Eveson JW, Reichart P, et al, eds. *World Health Organization Classification of Tumours. Pathology & Genetics Head and Neck Tumours*. Lyon: IARC Press, 2005:360.

Diseases of the Salivary Glands

John Wallace Eveson

Department of Oral and Dental Science, Bristol Dental Hospital and School, Bristol, U.K.

Toshitaka Nagao

Department of Diagnostic Pathology, Tokyo Medical University, Tokyo, Japan

I. ANATOMY

Salivary glands are tubulo-acinar exocrine organs responsible for the production and secretion of saliva. They comprise the three-paired major glands, the parotid, submandibular, and sublingual. There are also several hundred minor glands, which are widely distributed throughout the oral and oropharyngeal submucosa and, in some cases, the underlying muscle. Similar seromucous glands are present in the upper respiratory and sinonasal tracts.

The functional unit of salivary glands is the secretory acinus and related ducts and myoepithelial cells (Fig. 1A). Acini may be serous, mucous, or mixed. Serous acini form wedge-shaped secretory cells with basal nuclei. They surround a lumen that becomes the origin of the intercalated duct. The cytoplasm of serous cells contains densely basophilic, refractile zymogen granules that are periodic acid-Schiff (PAS) positive and diastase resistant. Their principal secretion is amylase. Mucous acinar cells also have basally placed nuclei, and their cytoplasm is clear and contains vacuoles of sialomucin (Fig. 1B). The secretions of these cells pass through the intercalated ducts. These are often inconspicuous in routine histologic sections. They are lined by a single layer of cuboidal cells with relatively large, central nuclei. They are continuous with the much larger striated ducts. These are lined by tall, columnar, eosinophilic cells that are rich in mitochondria. They have parallel infoldings of the basal cytoplasm and are responsible for modifying the salivary secretions. The striated ducts join the interlobular and excretory ducts. These are lined by pseudostratified columnar epithelium, which often contains scattered mucous cells. Luminal ductal cells are immunohistochemically positive for cytokeratins by CAM5.2 (1) and AE1/AE3, cytokeratin 1 (2), epithelial membrane antigen (3), and carcinoembryonic antigen (4).

Myoepithelial, or basket cells, are contractile and are located between the basement membrane and the basal plasma membrane of the acinar cells. They are

variable in morphology and are inconspicuous in hematoxylin and eosin-stained sections. Myoepithelial cells can be visualized with varying degrees of specificity by immunohistochemical staining for a wide range of antigens including S-100 protein, calponin, smooth muscle actin, smooth muscle myosin heavy chain (5–7) cytokeratin 14 (8), glial fibrillary acidic protein (9), h-caldesmon (10), maspin (11), metallothionein (12), and p63 (13). Although not specific, staining for p63, which is nuclear, is one of the most useful markers of myoepithelial cells in both normal and neoplastic tissue. Staining with myoid markers and cytokeratin 14 highlights the stellate shape of the myoepithelial cells (Fig. 1C). They have long dendritic processes that embrace the secretory acini. Myoepithelial cells also surround the intercalated ducts. Although cells in the abluminal layer of the striated ducts can be highlighted by “myoepithelial markers,” such as cytokeratin 14, the presence of true myoepithelial cells in this location is not firmly established. Ultrastructurally, the cytoplasm of typical myoepithelial cells contains actomyosin microfilaments running parallel with the outer surface of the cell, glycogen granules and lipofuscin, and pinocytotic vesicles may also be a conspicuous feature. Cells with these ultrastructural features are not seen in the striated ducts.

The parotid gland is almost purely serous and the parenchyma is divided into lobules by fibrous septa. There is abundant intralobular and extralobular adipose tissue, which increases in relative volume with age. In addition, the parotid gland contains lymphoid tissue in the form of about 3 to 24 lymph nodes and less structured lymphoid aggregates (14). The lymph nodes often contain salivary gland ducts or occasionally acini (Neisse Nicholson rests). Sebaceous glands, either individually or in small groups, are frequently seen in the parotid if the tissue is widely sampled (~40%) (Fig. 1D) (15). The presence of melanocytes has been reported in a single case (16). The submandibular gland is mixed serous and mucous, although the serous element predominates (~90%). In mixed acini, the serous cells form caps, or demilunes,

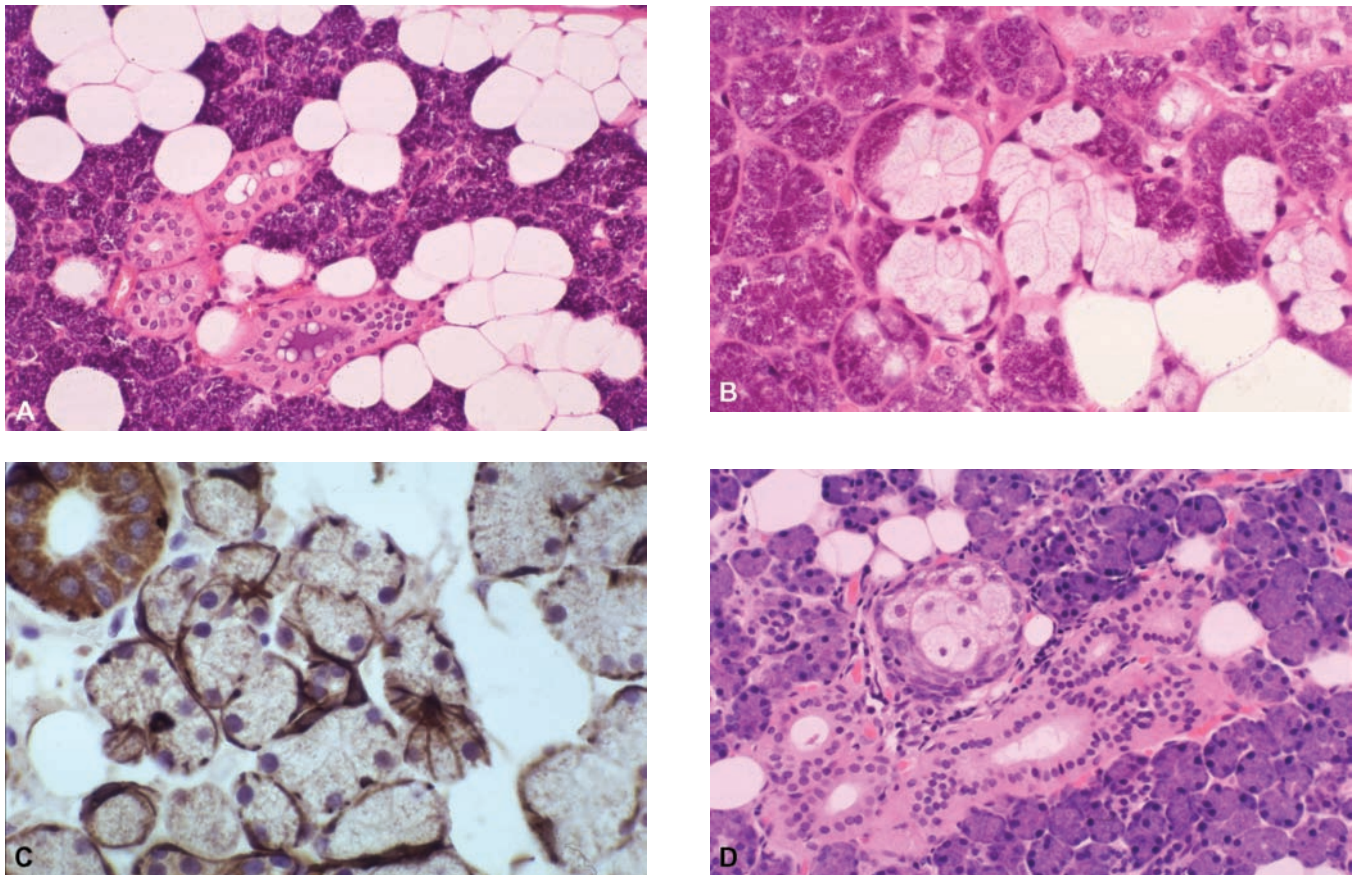


Figure 1 (A) Parotid gland showing purely serous acinar cells and conspicuous striated ducts. (B) Submandibular gland showing serous acinar cells forming demilunes over the mucous acinar cells. (C) Dendritic myoepithelial cells. Cytokeratin 14 stain. (D) Sebaceous gland in parotid gland.

on the periphery of the mucous cells. The intercalated ducts are shorter and the striated ducts more conspicuous than those of the parotid gland. Sebaceous cells are seen much less frequently in this gland (~5%) (15). The sublingual gland is predominantly mucous in type. The mucous acini form elongated tubules with peripheral seromucous demilunes. Sebaceous glands are only occasionally seen (~4%) (15).

Minor salivary glands are most numerous at the junction of the hard and soft palate, lips, buccal mucosa, tongue, floor of the mouth, and retromolar pad. They are present on the lateral aspects of the tongue, particularly in relation to the foliate papillae. In addition, minor glands are present in the ventral surface (glands of Blandin and Nuhn). These are typically located toward the midline and extend from the insertion of the tongue into the floor of the mouth to the tip. Glands in the lips and buccal mucosa are seromucous, whereas those in the ventral tongue, palate, glossopharyngeal area, and retromolar pad are predominantly mucous. Minor glands opening into the groove surrounding the circumvallate papillae (von Ebner's glands) are purely serous in type. The minor glands are not encapsulated, and those in

the tongue especially can be deeply located in the underlying muscle.

II. NONNEOPLASTIC DISORDERS

A. Developmental Defects

Aplasia, Hypoplasia, Atresia

Congenital aplasia of salivary glands, particularly the parotid gland, is very rare (1). It may be associated with other developmental abnormalities of the head and neck, especially those involving the first branchial arch. These include the lacrimo-auriculo-dento-digital (LADD) syndrome and aplasia of the lacrimal and salivary glands (ALSG), both of which appear to be caused by FGF10 mutations (2). An association between salivary gland aplasia and ectodermal dysplasia has also been described (3). Aplasia may be unilateral or bilateral and can cause severe xerostomia, candidosis, and accelerated dental caries. Hypoplasia of one or more glands may be less uncommon than previously considered, as cases are usually asymptomatic and are sometimes detected fortuitously in

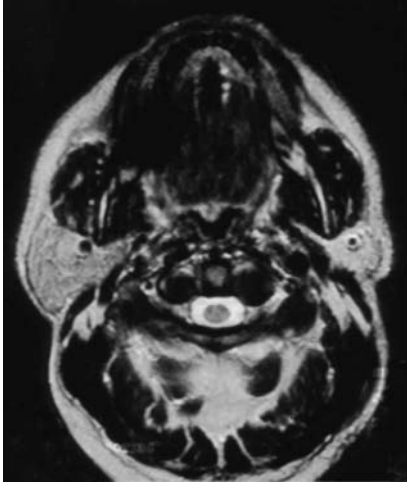


Figure 2 Magnetic resonance imaging scan showing a patient with an enlarged parotid gland due to sialosis and hypoplasia of the contralateral gland.

magnetic resonance imaging (MRI) scans (Fig. 2). Rare cases of salivary gland duplication have also been reported (4). Ductal atresia is also uncommon and affects Wharton's duct most frequently (5). In that site, it may cause cystic swellings in the floor of the mouth (6).

Heterotopia

Salivary gland tissue in sites other than its normal distribution is variously described as ectopic, heterotopic, or salivary gland choristoma (1). It is very common to see salivary ductal and acinar inclusions in the intra- and paraparotid lymph nodes (Fig. 3) (2).

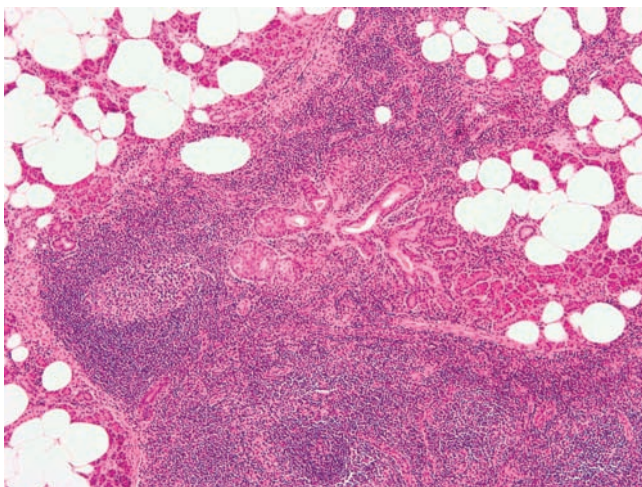


Figure 3 Intraparotid lymph node containing heterotopic salivary ducts and acini (Neisse Nicholson rests).

These are termed "Neisse Nicholson rests," and they may be important in the pathogenesis of Warthin's tumor and lymphoepithelial cysts (LECs). Heterotopic salivary tissue in other sites, however, is rare, and most cases involve the lower neck and middle ear. However, occasional examples have been described in a very wide range of sites, including the mandible and maxilla (3), gingiva (4,5), external auditory meatus (6), upper neck (7), thyroid and parathyroid gland and capsule (7–9), thyroglossal duct cyst (1), cerebellopontine angle (10), pituitary gland (11), mediastinum (12), stomach (1), skin (13), prostate gland (14), vulva (15), and rectum (16). The accessory salivary gland tissue that lies along the ducts of the major salivary glands, particularly the parotid, is considered to be a variation of normal anatomy rather than heterotopia (17,18).

Heterotopic salivary glands in the lower neck. Heterotopic salivary tissue in the lower neck is uncommon (19–21). Lesions typically present in the anterolateral border of the sternocleidomastoid muscle, usually close to the manubriosternal joint. They are frequently noticed shortly after birth but some cases may not present until much later in life. There is a single case report showing a familial association (22). Most cases are unilateral, and there is a predilection for the right neck. Rare, bilateral cases have also been reported. Some cases may be associated with a branchial cleft remnant on the contralateral side (2,21). The typical clinical presentation is the presence of a small sinus that may emanate from a cutaneous nodule. The sinus intermittently exudes small quantities of mucoid or watery, saliva-like fluid, particularly during meals.

Grossly, the sinus is usually less than 2 cm in length, and it communicates with a nodular or lobulated, gray-to-yellow mass that resembles normal salivary tissue (1). Microscopically, the tissue usually consists predominantly of anatomically normal mixed mucous and serous salivary acini, although occasionally it is purely serous. The salivary acini are surrounded by myoepithelial cells (21). There can be chronic inflammation and interstitial fibrosis due to extravasated mucus, and the associated ducts may show ectasia or squamous metaplasia. Occasionally there is cystic change (21). Very rarely, pleomorphic adenomas have developed in this tissue (23,24).

The embryologic origin of this heterotopic salivary tissue in the lower neck is contentious. In the branchiogenic theory, it is proposed that the tissue arises from the precervical sinus of His within the branchial arch system (19). This theory is supported by the anatomic location, congenital presentation, right-sided predilection with occasional bilateral cases, and the presence of predominantly mucous or mixed salivary acini (17,20,25). An alternative proposed origin is from a residue of the vagus nerve placodal duct (26,27).

Heterotopic salivary glands in the middle ear. Heterotopic salivary tissue in the middle ear is frequently termed salivary gland choristoma. It is rare, and since it was first described by Taylor and Martin in 1961 (28), less than 30 cases have been reported (29–35). They present in a wide age range (1–52 years)

with a mean of about 17 years (32). There is a female predominance of approximately 2:1. In addition, there is a striking left-sided prevalence. The most common presenting features are unilateral conductive hearing loss, otorrhea, and tinnitus. There is frequent ossicular deformity or absence, mainly affecting the incus and stapes, and abnormalities in the horizontal portion of the facial nerve, which may show dehiscence. Less common associated abnormalities include absence of the oval window, cholesteatomas (36), and malformations of the external ear (36,37).

Macroscopically, the lesion forms a smooth or bosselated, gray-to-yellow mass (1). It usually lies against, or close to, the facial nerve, which can make surgical excision challenging. Microscopically, it is composed of mixed mucous and serous acini and adipose tissue and variably present excretory ducts. The tissue is usually covered by normal respiratory type mucosa. Even incomplete excision is not associated with recurrence (31). Rare pleomorphic adenomas reported in the middle ear may have arisen from this tissue (38,39).

The pathogenesis of middle ear salivary chorioma has been linked with anomalous development of the first and second branchial arches before the fourth month of intrauterine development (40–43). Primordial salivary tissue becomes enclosed within the temporal bone and then grows within the middle ear until somatic growth ceases (37).

Intraosseous heterotopic salivary gland tissue. Salivary gland tissue is occasionally present within the mandible, and more rarely, the maxilla. The most common location is in the medial aspect of the mandible, anterior to the angle and below the mylohyoid line. An extension of the submandibular gland becomes partially incarcerated in a bony invagination. Less commonly, the defect contains only fat and fibrous tissue. This is symptomless and is usually detected fortuitously during radiographic investigations and a radiographic frequency of 0.48% has been reported (44). It appears as a sharply demarcated, cyst-like, radiolucent area with a corticated periphery and is known as a Stafne or static bone cavity (45–48). These defects are seen much more frequently in men (over 80%) and are typically discovered in the fifth and sixth decades. The pathogenesis of these lingual mandibular bone defects is uncertain. It has been suggested that part of the submandibular gland becomes entrapped within the mandible during development (49). However, this does not explain the age distribution of the patients. An alternative theory is that a lobe of the submandibular gland becomes hyperplastic and produces pressure atrophy of the adjacent mandible (50). Analogous defects are seen much less frequently in the lingual aspect of the anterior mandible (51,52). These also typically manifest in middle life with an unexplained 80% male predominance. They mostly present as unilateral radiolucent areas below or covering the roots of the canine or premolar teeth and can mimic a radicular cyst (53). A small number form midline radiolucencies associated with the incisor teeth. There is a bony depression containing

predominantly mucous salivary tissue that is usually in continuity with the adjacent sublingual gland.

Heterotopic salivary gland tissue elsewhere in the jaws, particularly within marrow spaces, has rarely been reported. In a study of 5034 marrow samples, 13 cases (0.3%) contained heterotopic salivary tissue (3). An additional four cases were found in the condyle. Sampling limitations in such a study mean that the true frequency of intraosseous heterotopic salivary tissue is likely to be much higher. Although uncommon and typically symptomless, intrabony heterotopic salivary tissue may be the source of primary intraosseous (central) salivary gland tumors (3). [See the section "Intraosseous (Central) Tumors."]

Polycystic (Dysgenetic) Disease

This is a very rare condition of developmental origin characterized by the formation of multiple cysts, usually in one or both parotid glands (1–4). A single case has been reported bilaterally in the submandibular glands (5). Most patients (90%) are female, and there are two case reports of a familial association (1,4), suggesting an autosomal dominant mode of transmission. Symptoms typically begin in childhood and include recurrent, painless parotid gland swellings at mealtimes. There is no associated clinical abnormality of salivation.

Microscopy shows preservation of the lobular architecture, but the salivary parenchyma is extensively replaced by a honeycomb of cysts of varying sizes. These appear to be derived from the intercalated ducts. Between the cysts, there is residual parenchyma, excretory ducts, and interlobular septa. The cysts are lined mainly by cytologically bland cuboidal or more flattened cells. Some lining cells may be oncocytic or vacuolated, and there may be luminal apocrine blebbing. Foci of mural thickening can give a pseudopapillary appearance. Some cysts show narrowing, producing an hourglass shape (Fig. 4). Incomplete septa extending into the cystic lumina are another characteristic appearance (Fig. 5). The cyst lining may fuse with striated ducts or distended acini. The cysts may contain amorphous eosinophilic material or concentrically laminated spheruliths. There is usually no inflammatory component.

The microscopic differential diagnosis includes sclerosing polycystic adenosis, cystadenoma, and cystadenocarcinoma. The generalized nature of polycystic (dysgenetic) disease, the clinical history, and characteristic microscopic features mean that making a definitive diagnosis is unlikely to be problematic.

The condition is benign, and treatment need only be used for cosmetic reasons.

Cystic Fibrosis (Mucoviscidosis)

Cystic fibrosis is a life-threatening disease that is inherited as an autosomal recessive trait. It involves most exocrine, mucous-secreting glands including the salivary glands. There is secretion of abnormally viscous mucus that produces duct obstruction and consequent

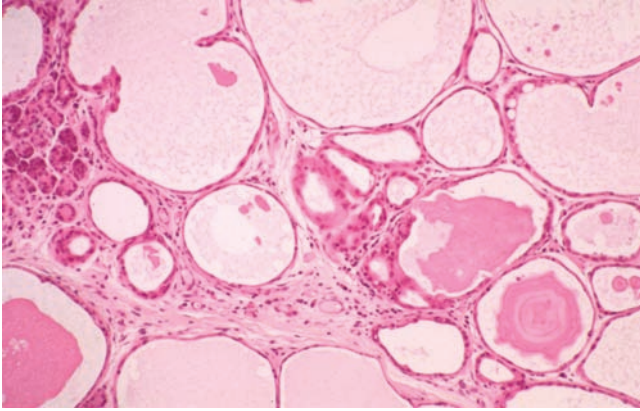


Figure 4 Polycystic (dysgenetic) disease showing parotid tissue extensively replaced by multiple cysts, some of which show central constrictions (hourglass shape). In addition there are concentrically laminated spheruliths.

parenchymal atrophy. The submandibular, sublingual, and minor salivary glands may be involved, but the purely serous parotid gland is rarely, if ever, affected (1). The sublingual gland is the most severely affected, but most histologic studies have been undertaken on minor labial glands where the changes are extremely variable and many glands appear normal (2–4). There is occlusion of the dilated ducts and glandular acini by inspissated, eosinophilic material, which may be concentrically laminated (Fig. 6). Some of the ducts, especially in the sublingual gland, contain microliths consisting of mucoprotein and calcium complexes. There is chronic inflammation and interstitial fibrosis, together with acinar atrophy. Despite the sometimes striking histologic changes in these glands, oral symptoms are uncommon and mild.

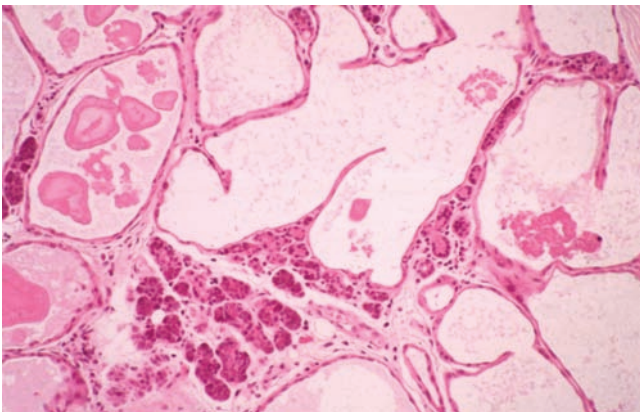


Figure 5 Polycystic (dysgenetic) disease showing incomplete septa extending into the cysts, and residual salivary acini.

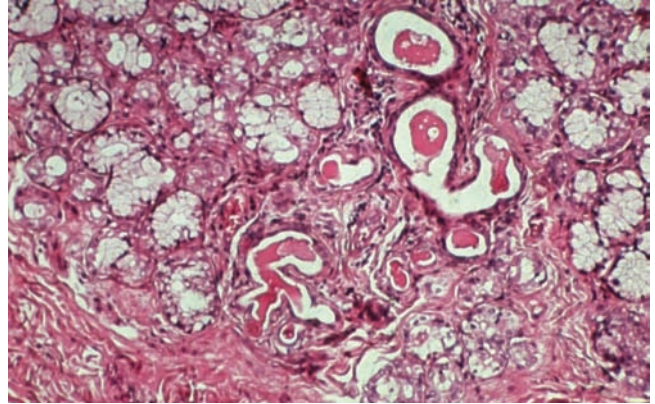


Figure 6 Mucoviscidosis. Minor salivary gland biopsy shows ductal dilatation, eosinophilic plugs, and acinar atrophy.

Sebaceous Glands

Sebaceous differentiation is common in normal major salivary glands, with an incidence of 10% to 42% in parotid glands, 5% to 6.4% in submandibular glands, and 4.2% of sublingual glands (1–3). The higher incidence of sebaceous elements in the parotid gland has been related to its origin from ectoderm compared with the probable endodermal origin of the submandibular and sublingual glands (1). The frequency of sebaceous foci varies with age with bimodal peaks between the ages of 10 and 20 years and individuals over 70 years of age (2,4,5). There is no sex predilection. Sebaceous cells may appear as isolated cells in the walls of intercalated or striated ducts or form recognizable sebaceous glands that are connected to these intralobular ducts (Fig. 7). Cells at the periphery of the gland are flattened and have round or oval nuclei, and central cells have abundant, vacuolated cytoplasm, rich in lipids, and irregular or pyknotic nuclei (1). The holocrine secretion eventually

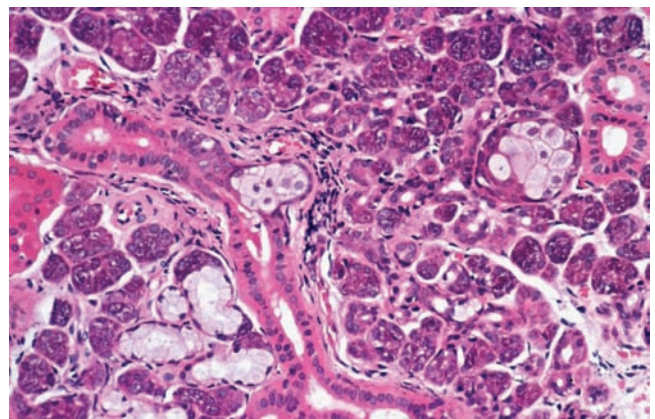


Figure 7 Sebaceous cells in submandibular gland.

discharges into the duct and is mixed with saliva. Sebaceous foci have been described in chronic sialadenitis and in salivary gland tissue adjacent to salivary tumors, but this association is probably coincidental. The increased frequency of sebaceous glands during and after puberty may result from hormonal factors (3); however, the functional significance of these sebaceous elements is not known.

B. Salivary Gland Cysts

Mucocoeles

Mucocoeles are the most common cystic lesions of salivary glands, and almost all form in the minor glands. The main types are extravasation, retention, and superficial.

Extravasation mucocoeles account for the large majority of mucocoeles (~90%). They are seen most frequently in children and young adults. Although they are considered to be caused by trauma to a gland or an excretory duct with escape of salivary secretions into the surrounding tissues, only a minority of patients can recall a traumatic episode. It has recently been suggested that rupture of adjacent lymphatic vessels may play a role in the pathogenesis (1). The most frequent site is the lower lip (~50%). Other common sites include the buccal mucosa, floor of the mouth and ventrum of the tongue (glands of Blandin and Nuhn), and palate and buccal mucosa (2). They occasionally present in the retromolar pad and gingiva. Mucocoeles usually present as a bluish, domed swelling, which rarely exceeds 1 cm in diameter except in the floor of the mouth. The cysts may fluctuate in size, and in some cases, there is spontaneous regression due to progressive scarring of the affected gland. Mucocoeles in the floor of the mouth are termed "ranulae" and can be several centimeters in diameter. The peak incidence of extravasation mucocoeles is in the second and third decades, and occasional cases are multiple (3).

In the early stages of development, microscopy shows ill-defined pools of mucus and acute inflammation. Occasionally, a portion of damaged excretory duct is visible. A central cavity becomes more defined, and the cyst becomes lined by granulation tissue, which undergoes progressive fibrosis (Fig. 8). The cyst eventually becomes lined by compressed macrophages, many containing abundant mucus (muciphages), and similar cells can be seen floating freely in the cyst cavity (Fig. 9). In developing mucocoeles, the true character of the process may not be immediately apparent unless muciphages are identified, either as foamy macrophages in hematoxylin and eosin-stained sections or by histochemical stains. Treatment is by excision of the cyst and related salivary gland or by cryosurgery. Cysts in the tongue, especially, have a significant tendency to recur, probably because the associated minor glands are mainly located deeply within the lingual musculature. Mucocoeles in the upper lip are uncommon (~5%), and the possibility of a cystic salivary gland neoplasm should always be considered when examining cystic lesions from this site.

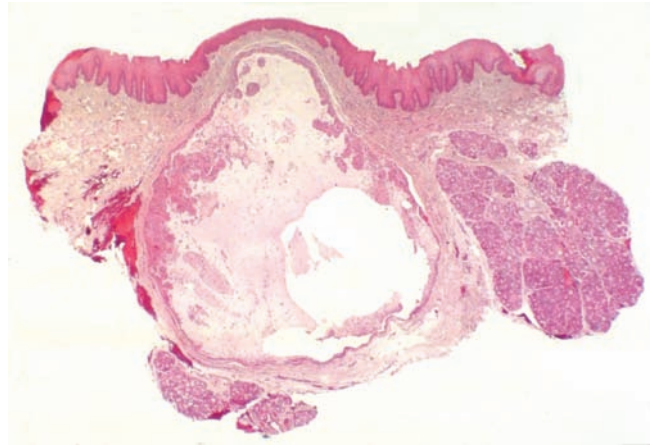


Figure 8 Extravasation mucocoele showing cyst lined by cellular fibrous tissue and macrophages (muciphages) with adjacent minor salivary gland.

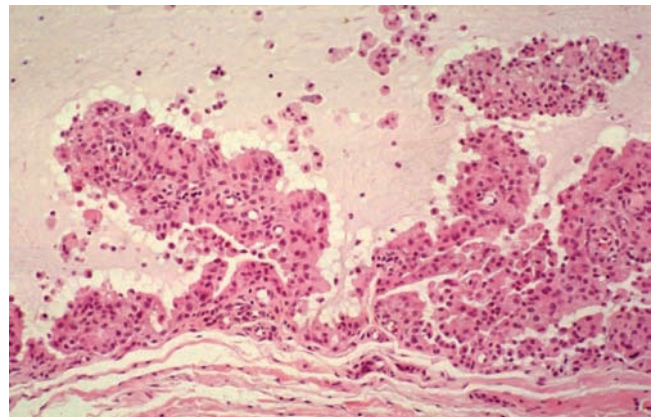


Figure 9 Extravasation mucocoele: higher power showing compressed fibrous tissue, and mucocytes in the wall and floating freely in the cyst cavity.

Mucous retention cysts are relatively uncommon and are usually seen in older individuals (4). The cause is uncertain but may be related to intermittent duct obstruction. They form unicystic cavities that are lined by modified duct epithelium, which may be cuboidal or columnar and occasionally shows squamous or mucous metaplasia (Fig. 10) (4). Rarely there is oncocytic metaplasia (5).

Some mucocoeles are located immediately below the epithelium and raise a small blister (6). These are known as superficial or subepithelial mucocoeles (Fig. 11). They are seen most frequently in the region of the palatoglossal fold, but they can be found elsewhere in the mouth, including the gingiva. They are often multiple and appear to be much more common in women rather than men. Cases have been reported in association with lichen planus and

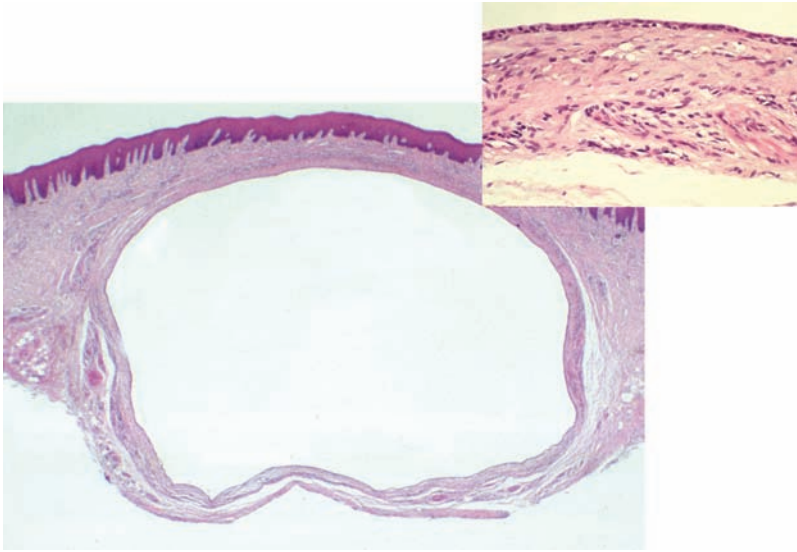


Figure 10 Retention mucocele lined by attenuated epithelium.

graft-versus-host disease (7,8). In clinical practice, these lesions are not uncommon. Because they form subepithelial blisters, they are sometimes confused with mucocutaneous vesiculating disorders, especially mucous membrane pemphigoid and bullous lichen planus, both clinically and microscopically.

Salivary Duct Cyst

Salivary duct cysts (sialocysts) are a rare type of retention cyst seen in the major salivary glands, particularly the parotid (9). They may be associated with an obvious duct obstruction, and occasionally, the cyst itself leads to obstructive symptoms. There is no sex predilection, and most patients are in their fourth decade or older. The cyst usually presents as a unilocular, painless swelling that rarely exceeds 3 cm in diameter.

Microscopically, they usually have a patchily inflamed, thick, fibrous wall lined by stratified squamous, columnar, or cuboidal epithelium (Fig. 12). There may be focal mucous or oncocytic metaplasia. Occasionally, there is partial calcification of the cyst contents, and granulomatous inflammation may be present in the cyst wall and adjacent gland. Complete surgical excision is curative.

Lymphoepithelial Cyst

Lymphoepithelial cysts (LECs) are uncommon, and most arise in the parotid gland although microscopically similar lesions have been described in the anterior floor of the mouth (10,11).

The proposed origin of these cysts from the branchial arch system (12) has been disputed and an

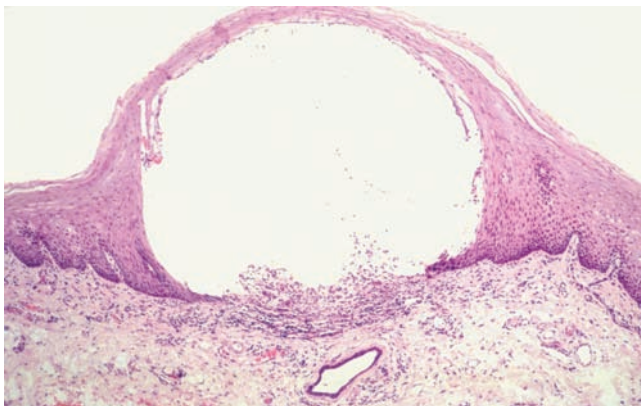


Figure 11 Superficial mucocele. There is a subepithelial blister with overlying attenuated epithelium. The duct of a minor salivary gland is visible under the floor of the blister.

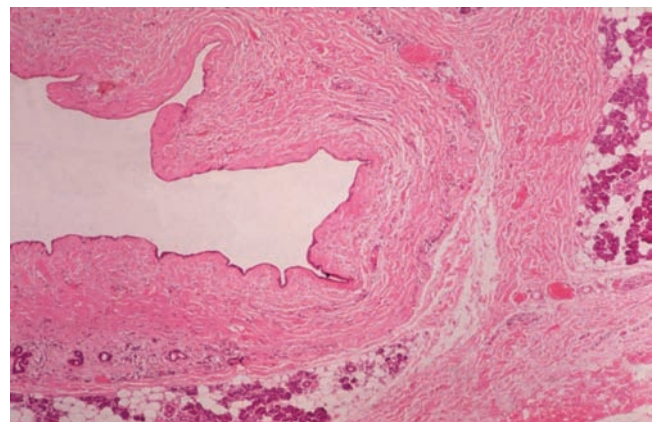


Figure 12 Salivary duct cyst. Low-power view showing a thick, fibrous-walled cyst lined by a double-layered columnar epithelium.

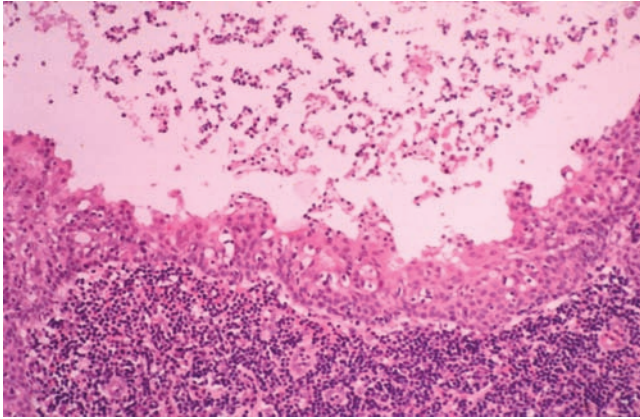


Figure 13 Lymphoepithelial cyst lined by irregular stratified squamous epithelium with a dense lymphoid infiltrate in the cyst wall.

origin from Neisse Nicholson rests appears to be more likely (13,14). They resemble salivary duct cysts in clinical presentation, and the average age of patients is 45 years. Microscopy shows an epithelial-lined cyst with dense lymphoid aggregates containing prominent germinal centers in the cyst wall (Fig. 13). The epithelial lining is usually stratified squamous, but there may be focal areas of cuboidal or respiratory-type epithelium, and both mucous and sebaceous metaplasia have been reported (15,16).

C. Infiltrations

Lipomatosis

Fat is a normal but highly variable component of the parotid gland and, to a much lesser extent, the submandibular, sublingual, and minor salivary glands. The fat content appears to increase with age, in obese individuals and those with diabetes. The fat is distributed interstitially and separates the salivary parenchyma. There may be fatty infiltration and replacement of atrophic parenchyma for any cause, but this is most commonly seen in chronic obstructive sialadenitis (Fig. 14). Increased fat deposition has also been reported in Sjögren's syndrome using *in vivo* techniques (1). Occasionally, almost the whole of the parotid or submandibular gland is replaced by fat (lipomatous salivary atrophy). Seifert (2) described a case of lipomatous parotid atrophy in a child with lipomatous pancreatic atrophy and speculated on an association with coxsackie B virus. Some cases in infants have been rapidly progressive (3). A case of salivary lipomatosis has also been reported in a minor gland (4).

Oncocytic Lesions

Introduction. The term "oncocyste," which is derived from the Greek word *oukoustai* meaning "to swell," was first coined by Hamperl in 1931 (1). These

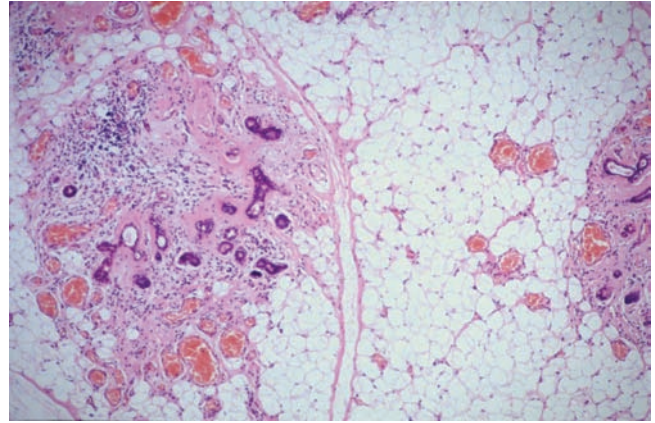


Figure 14 Obstructive sialadenitis with acinar atrophy, interstitial fibrosis and extensive fatty infiltration.

cells are characterized by abundant granular and brightly eosinophilic cytoplasm, which contains increased numbers of mitochondria. The nuclei are typically round and centrally placed, and the nucleoli are usually single and conspicuous. The cells are generally cuboidal or polygonal, and there is a low nuclear-cytoplasmic ratio. In contrast to this type of "light" form of oncocytic cell, some oncocytes have more intensely staining, eosinophilic cytoplasm and densely basophilic, shrunken nuclei. These are termed "dark" cells, or pyknocytes; they are probably a degenerative form of the light cell. Oncocytic cytoplasmic granules stain positively with phosphotungstic acid hematoxylin after 48 hours incubation. The mitochondrial nature of the granules has been confirmed by staining with antimitochondrial antibodies (2) and electron microscopy (3). It has been speculated that oncocytosis and oncocytic neoplasia are the result of progressively acquired mitochondriopathies due to mtDNA errors (4).

Focal and diffuse oncocytosis. Focal oncocytosis of ducts, and less commonly acini, is common in both major and minor salivary glands with increasing age (Fig. 15A). It is rare in patients younger than 50 years, common in patients between 50 and 70 years and virtually always present in older individuals (5,6). Diffuse oncocytosis of the parotid gland, however, is rare and may be bilateral (Fig. 15B) (7–10). The entire gland, including both ducts and acini, can be involved. There are both light and dark oncocytic cells. This condition affects elderly patients and may be associated with fatty infiltration and acinar atrophy (11).

Ductal oncocytosis. There may be extensive ductal oncocytosis with associated dilatation in minor glands, particularly in the larynx (Fig. 15C) (see Chapter 3). This is less common in the oral cavity, where the floor of the mouth is the usual location. It usually presents clinically as a small, painless mass. Microscopy shows unilocular or multilocular dilated ducts

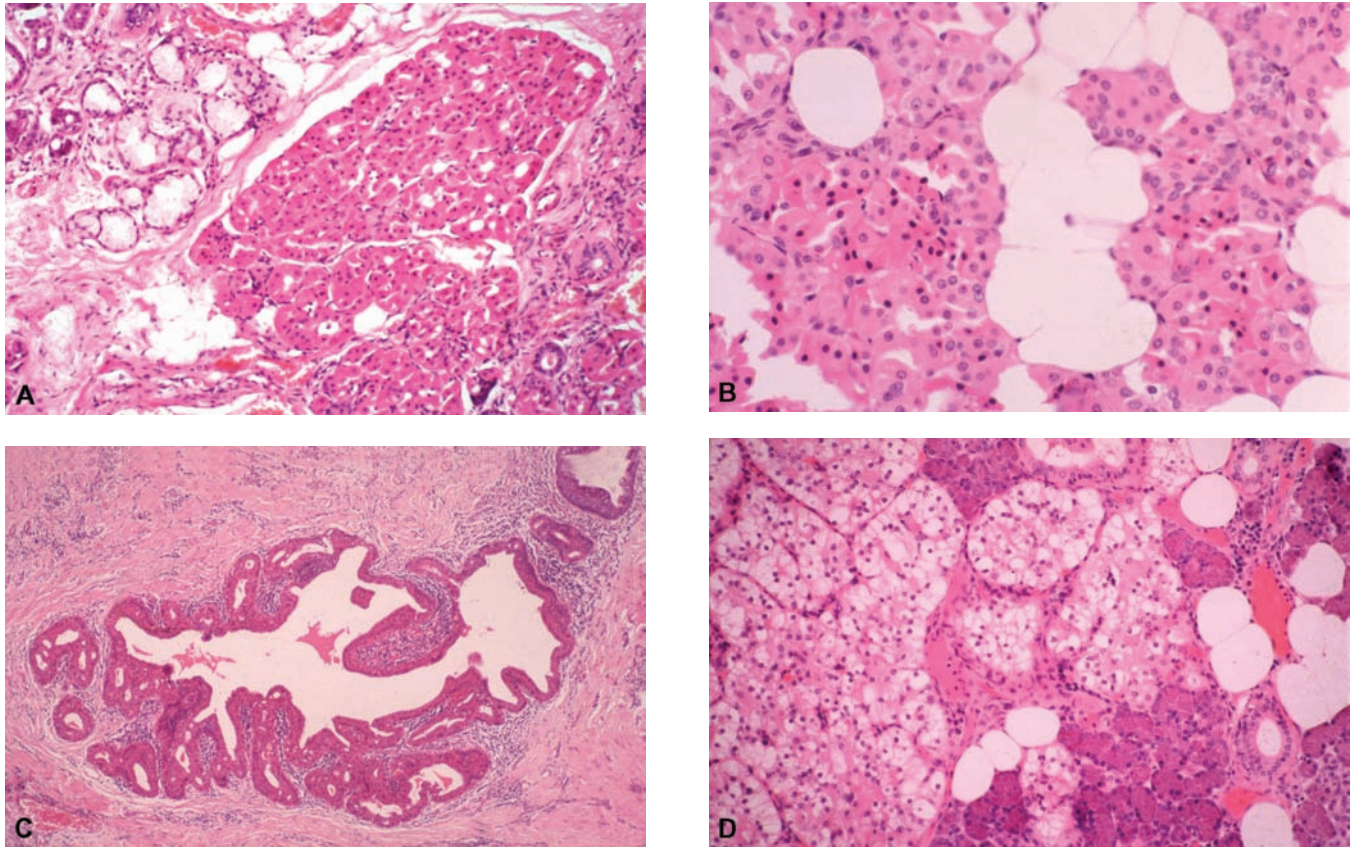


Figure 15 (A) Focal oncocytosis. (B) Diffuse oncocytosis involving the entire parotid gland and showing characteristic light and dark cells. (C) Ductal oncocytosis and hyperplasia in minor salivary gland. (D) Multifocal nodular oncocytic hyperplasia that gives an erroneous impression of invasion of surrounding salivary parenchyma.

lined by cytologically bland, oncocytic, and columnar epithelium. There may be luminal papillary ingrowths. The lesions are not encapsulated and can be multifocal. There is often a stromal chronic inflammatory component, and in some cases, this can result in a Warthin-like appearance of the lesion.

Multifocal nodular oncocytic hyperplasia. Multifocal nodular oncocytic hyperplasia (MNOH) is a rare condition that is characterized by the presence of multiple nodules of oncocytic cells (11,12). The nodules have a lobular distribution, and at the edges of the nodules, cells may appear to engulf or invade the surrounding normal salivary gland parenchyma (Fig. 15D). In addition, islands of oncocytic cells can pervade the hila of intraparotid lymph nodes giving the erroneous impression of metastatic spread (Fig. 16). Some or all of the oncocytic cells can have clear cytoplasm, and this appearance has been termed clear cell oncocytosis (13). MNOH can be seen in association with an oncocytoma, and the distinction from a large hyperplastic nodule may be difficult or impossible.

It has been postulated that hyperplastic nodules are less organized and circumscribed than oncocytomas (14) and that oncocytomas should have at least a

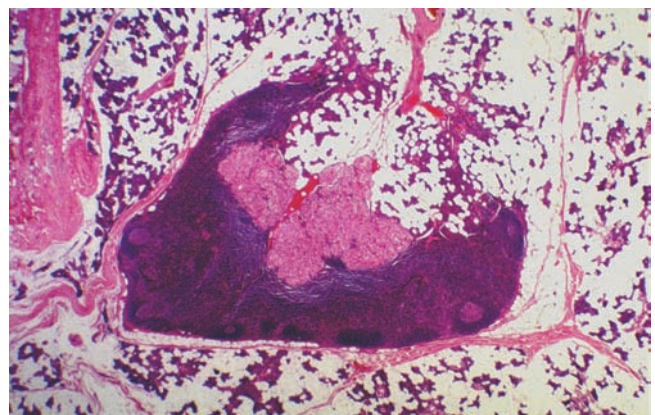


Figure 16 Multifocal nodular oncocytic hyperplasia involving the hilum of an intraparotid lymph node.

partial fibrous capsule (11). MNOH may also be seen in combination with other benign or malignant salivary gland tumors, particularly pleomorphic adenoma (11).

Amyloidosis

Amyloidosis of salivary glands appears to be rare, and in some large series, no cases of clinical salivary involvement were found (1,2). Localized amyloidosis has been reported in the parotid (3), submandibular (4) and sublingual glands (5). Both major and minor salivary gland involvement can be seen in systemic amyloidosis, which can be primary or secondary. In primary amyloidosis, there is an immunocyte dyscrasia that results in excess production of abnormal light chain immunoglobulin (AL-type amyloid). This overproduction is usually associated with multiple myeloma or is idiopathic. Extensive amyloid deposition has been reported in association with an extramedullary plasmacytoma within the parotid gland (6). Amyloidosis is occasionally seen in patients presenting with primary Sjögren syndrome (7,8). Secondary or reactive amyloidosis (AA-type amyloid) is due to long-standing chronic inflammatory diseases such as rheumatoid arthritis and tuberculosis and can be associated with a variety of carcinomas. Although there are few cases of clinical salivary gland involvement in secondary amyloidosis, deposits of amyloid have been detected in labial salivary glands in the large majority of cases (9,10).

Microscopy shows replacement of salivary parenchyma by homogeneous, eosinophilic material, patchy chronic inflammation, and sporadic multinucleated giant cells (Fig. 17). The amyloid shows orange staining with Congo and Sirius red stains, and there is characteristic green/orange birefringence under polarized light. In minor salivary glands, the amyloid deposition is predominantly periductal or periacinar, with less frequent perivascular or interstitial deposition (9).

Iron Deposition

In hemochromatosis, iron can be deposited as hemosiderin in both major and minor salivary glands, leading to a clinical presentation similar to primary

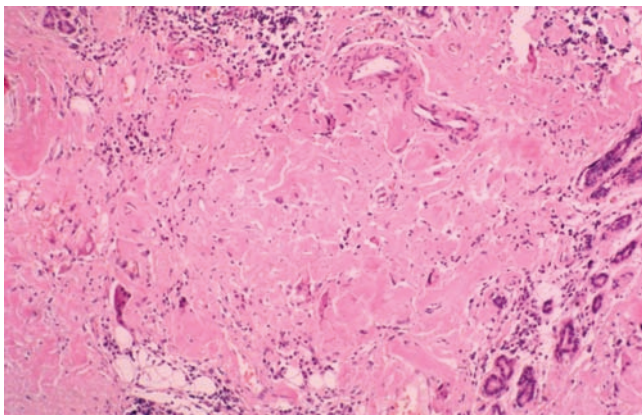


Figure 17 Amyloidosis of submandibular gland showing extensive acinar destruction by globular hyaline deposits and patchy chronic inflammation.

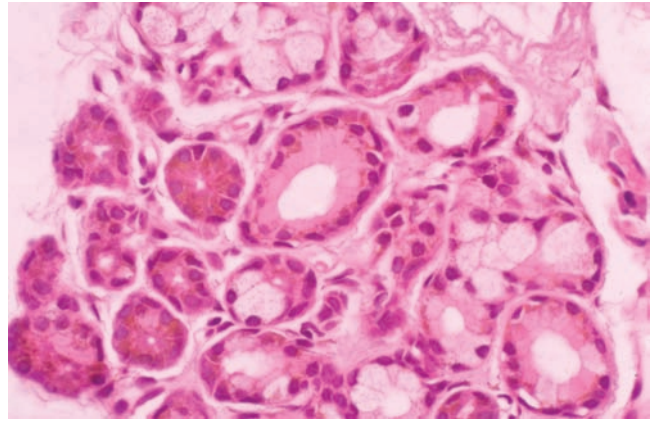


Figure 18 Hemochromatosis in minor labial gland biopsy showing granular, golden-brown hemosiderin deposition.

Sjögren syndrome (1–3). It can also be a feature of thalassemia major, with or without secretory impairment, usually in patients receiving multiple transfusions (4–6). Histologic changes include acinar atrophy, duct dilatation, interstitial fibrosis, and mild chronic inflammation. Reddish-brown hemosiderin deposits are seen in ducts and at the periphery of acinar cells (Fig. 18). They can be visualized more easily by using a Perl's Prussian blue stain. Iron deposition in lower labial salivary gland biopsies has been used to establish early diagnosis in neonatal hemochromatosis (7), allowing prompt medical intervention. In these patients, the histologic features are more subtle, as the gland structure is relatively unchanged and the amount of intracellular hemosiderin deposition may be minimal.

D. Sialadenitis

Acute Suppurative Sialadenitis

Acute suppurative sialadenitis most frequently involves the parotid gland followed by the submandibular gland. This may be explained because the serous saliva produced by the parotid gland has less bacteriostatic activity than that of the mucinous saliva of the submandibular gland. The reduction of the secretory flow and stasis of saliva, typically as a result of dehydration, is an integral pathogenetic factor of acute suppurative sialadenitis (1–5). Acute bacterial submandibular infection often is associated with obstruction of Wharton's duct by stones or strictures.

Although acute suppurative parotitis can occur in individuals of any age, patients aged from 50 to 70 years are the most frequently affected, with an equal sex distribution. Parotid infections are occasionally observed in premature infants who have a greater propensity for dehydration than term infants. Acute suppurative sialadenitis accounts for 0.03% of hospital admissions, with 30% to 40% of these occurring in

postoperative patients (5). Acute postoperative parotitis is often observed in patients with debilitating disease or postoperative complications, particularly after major gastrointestinal surgery. Predisposing factors are dehydration, malnutrition, oral neoplasms, liver cirrhosis, and diabetes mellitus (1–5). The use of drugs with an antisialogogue action, the most common being tricyclic antidepressants and diuretics, has been also associated with acute suppurative sialadenitis.

In acute suppurative sialadenitis, bacterial organisms usually enter from the oral cavity in a retrograde fashion. *Staphylococcus aureus* is the most common causative agent, and accounts for 50% to 90% of cases (1–5). Other aerobic organisms cultured from the disease include *Streptococcus pneumoniae*, *Streptococcus pyogenes* (β -hemolytic *Streptococcus*), *Streptococcus viridans*, *Hemophilus influenzae*, *Klebsiella pneumoniae*, and *Escherichia coli*, and *Pseudomonas aeruginosa*. Methicillin-resistant *Staphylococcus aureus* (MRSA) has also been reported. More recently, anaerobic organisms in acute salivary infections have been recognized, including *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium* species. Acute suppurative parotitis is usually a unilateral disease, but 10% to 25% of cases have been bilateral involvement (3). The usual clinical presentation is sudden onset of diffuse swelling of the affected gland associated with tenderness, induration, erythema, and pain. Some patients complain of limited movement of the mandible and difficulty in swallowing. Patients frequently have systemic signs of toxemia, including delirium, high fever, and leukocytosis. Association with systemic sepsis is far more common in infections of the parotid gland than in those of the submandibular gland. The respective intraoral duct orifice may become red and swollen with purulent discharge recognized on massage of the gland. Fluctuation of the parotid gland does not occur until late in the course of the disease because of the presence of multiple investing fascias enveloping the gland. The infection can extend locally by rupture of the abscess into surrounding tissues, resulting in osteomyelitis and fistula formation. The diagnosis of acute suppurative sialadenitis is based on the clinical presentation with culture of the purulent material from the duct. Any abscess formation can be located using ultrasound or computerized tomography (CT) scanning. Sialograms are contraindicated in cases of acute suppurative infection of the salivary glands. Patients with acute suppurative sialadenitis may eventually develop profound dehydration, sepsis, and multiorgan system failure.

Initial treatment of acute suppurative sialadenitis should be conservative, with eliminating the causes, improved oral hygiene, adequate hydration to increase the salivary flow, repeated massage of the affected gland, and administration of appropriate oral or intravenous systemic antibiotics, usually for a penicillinase-resistant *Staphylococcus*. Irradiation of the glands is no longer recommended. In cases involving abscess formation, incision and drainage by surgical intervention are indicated.

Histologically, early acute suppurative sialadenitis is characterized by edema, hyperemia, and an

accumulation of bacteria and neutrophils. As the inflammatory process progresses, marked periductal and interstitial neutrophilic infiltration with development of microabscesses leads to destruction of the ductal epithelium with necrosis and loss of the acinar tissue and eventually macroabscess and fistula formation.

Obstructive Sialadenitis and Sialolithiasis

Introduction. Obstructive sialadenitis is the most frequent type of chronic sialadenitis, accounting for about 30% of all chronic sialadenitis cases and approximately 1% of all salivary gland diseases (1,2). Although sialolithiasis is by far the most common cause of obstructive sialadenitis, there are two major factors playing a role in the pathogenesis of the disease (2). One is a mechanical obstruction by sialoliths, salivary gland cysts and tumors, and lesions of the oral mucosa. The other factor is a disturbance of the electrolyte concentration of saliva, resulting in the development of viscous secretory products. Most sialoliths, also referred to as salivary calculi or stones, are composed primarily of calcium phosphate together with an organic matrix of various amino acids and carbohydrates (1,3,4). Sialoliths develop as a result of deposition of calcium salts around a nidus such as bacterial colonies, cellular debris, mucous plugs, or foreign bodies. The precise cause of the development of sialoliths has not been fully elucidated, but infection or inflammation of the ducts as well as increased viscosity and stasis of saliva have been suggested as predisposing factors (3,4). Gout is associated with the formation of sialoliths, in which case, they are composed of uric acid.

Clinical features. The peak age of incidence of sialolithiasis is between 30 and 60 years, with a mean of about 45 years (1). Its occurrence in patients younger than 20 years, or older than 70 years, is rare. There is a slight male preponderance. About 80% of cases of sialolithiasis develop in the submandibular gland, followed by less than 20% in the parotid gland. Involvement of the sublingual and minor salivary glands is relatively rare (1). The upper lip and buccal mucosa are the most common minor salivary gland sites. The submandibular gland is more susceptible to sialolithiasis than the other salivary glands because its saliva has higher mucin content, increased viscosity, a more alkaline pH, higher concentrations of calcium and phosphate, and antigravity flow within the duct (5). In the majority of patients with sialolithiasis, only a single stone is found. Multiple stone formation involving unilateral or bilateral glands is uncommon. Sialoliths may be present both within the main ducts and within the gland parenchyma. In the submandibular gland, 57% of stones are localized near the hilum, 34% in the distal area of the submandibular duct (Wharton's duct), and 9% in the intraglandular ducts (6). The formation of sialoliths in the main ducts produces swelling of the distal salivary gland tissue with or without pain. The episodes of the symptoms are frequently recurrent and exacerbated by eating. There are distinct correlations between the severity of

the symptoms and the degree of obstruction. When sialoliths occur in the submandibular gland duct, induration can be observed in the floor of the mouth, and the duct orifice becomes erythematous and swollen. Sialoliths in the minor salivary glands are mostly asymptomatic presenting as a small, firm nodule. Sialoliths of intraglandular ducts of the major salivary glands also may not cause significant clinical symptoms. The complications of sialolithiasis include acute suppurative sialadenitis, ductal ectasia, and stricture. Ductal obstruction blocks secretion and leads to stasis of the saliva within the duct, which becomes predisposed to retrograde bacterial infection; *Streptococcus viridans* is a commonly involved pathogen. In such instances, mucopurulent material may be produced from the duct orifice by massaging the involved gland.

The diagnosis of sialolithiasis is principally based upon clinical and imaging examinations (3,6). Sialoliths of the distal area of Wharton's duct and the hilum can be detected by bimanual palpation of the affected area. Plain radiography is a helpful method to diagnose sialolithiasis, but 90% of submandibular stones are radiopaque while most parotid stones are radiolucent. In addition, intraparenchymal sialoliths may be difficult to visualize. Sialography is very accurate in the diagnosis of sialolithiasis but is usually unnecessary and is contraindicated in the acute setting of sialadenitis. Instead, high-resolution ultrasound and CT are the most useful diagnostic tools.

The first steps of management of sialolithiasis in the submandibular and parotid glands include conservative methods, such as adequate hydration, sialogogues, and gland massage as well as minimally invasive approaches, such as basket retrieval and interventional sialendoscopy to remove the stones, depending on their location and size (3,6). When these measures fail, extracorporeal shock wave lithotripsy may be the treatment of choice. Extirpation of the affected gland is recommended only in the minority of recalcitrant cases.

Pathology. Histologically, obstructive sialadenitis is characterized by ductal obstruction accompanied by a periductal chronic inflammatory cell infiltrate and fibrosis, ductal ectasia, and varying degrees of acinar atrophy (Fig. 19) (1,2,7,8). The initial alterations are duct ectasia containing viscous masses of secretory products and development of microliths. The persistence and progress of the obstructive process cause periductal sclerosis, increased acinar atrophy, and eventually destruction of the lobular architecture, resulting in loss of secretory function of the gland. There may be squamous, mucous cell, and oncocytic metaplasia of the duct epithelium. These features can simulate mucoepidermoid carcinoma, but obstructive sialadenitis lacks an infiltrative nature and the presence of intermediate cells characteristic of mucoepidermoid carcinoma. Ducts may contain sialoliths, which vary in color from white to yellow-tan (Fig. 20A) and consist of concentric laminations of calcification (Fig. 20B), often with organic debris at the center. A foreign body granulomatous reaction is commonly caused by extravasation of secretory ductal

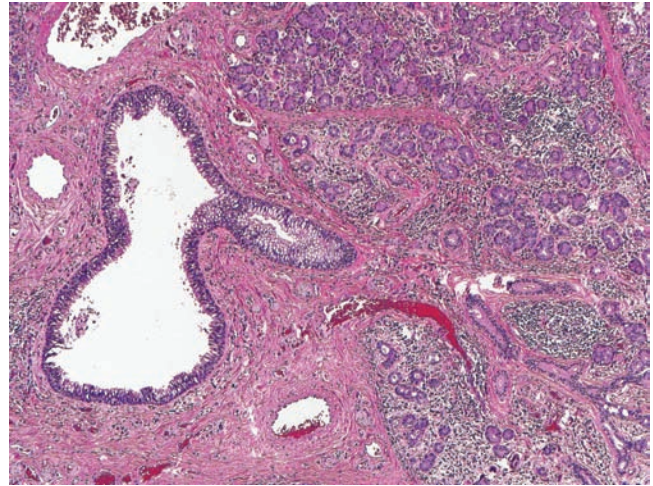


Figure 19 Obstructive sialadenitis of the submandibular gland. Ductal ectasia with periductal fibrosis accompanied by chronic inflammatory cell infiltrate and acinar atrophy.

contents into the interstitial tissue. Complications of obstructive sialadenitis include acute suppurative inflammatory change with abscess formation, in addition to sinus tract and salivary fistulae.

On immunohistochemistry, CD4-positive lymphocytes, which are the predominant subsets, are located mainly periductally (9). Isolated intraepithelial CD8-positive cytotoxic T cells are associated with ductal epithelial cell destruction. B lymphocytes are restricted to lymphoid follicles located periductally and around intralobular ducts.

Chronic Sclerosing Sialadenitis (Küttner Tumor)

Introduction. Chronic sclerosing sialadenitis is an inflammatory disease of the salivary glands, which was first described by Küttner in 1896 (1). It has also been referred to as Küttner tumor, because chronic sclerosing sialadenitis produces a hard swelling of the salivary gland that cannot be easily distinguished clinically from neoplasia. This inflammatory process almost exclusively affects the submandibular gland. Although chronic sclerosing sialadenitis is a fairly common type of chronic sialadenitis in the submandibular gland, it has been underrecognized by many clinicians and pathologists for many years because of few reports in the English literature (2).

The exact etiology of chronic sclerosing sialadenitis remains unknown. While sialolithiasis is frequently associated with chronic sclerosing sialadenitis, occurring in 29% to 83% of cases, the progression of the inflammatory process, such as the intense lymphocytic infiltration, the formation of lymph follicles, and the destruction of salivary ducts in the submandibular gland could not be explained pathogenetically by purely obstructive mechanisms (2-4). Thus, sialolithiasis may be a secondary response by a functional abnormality

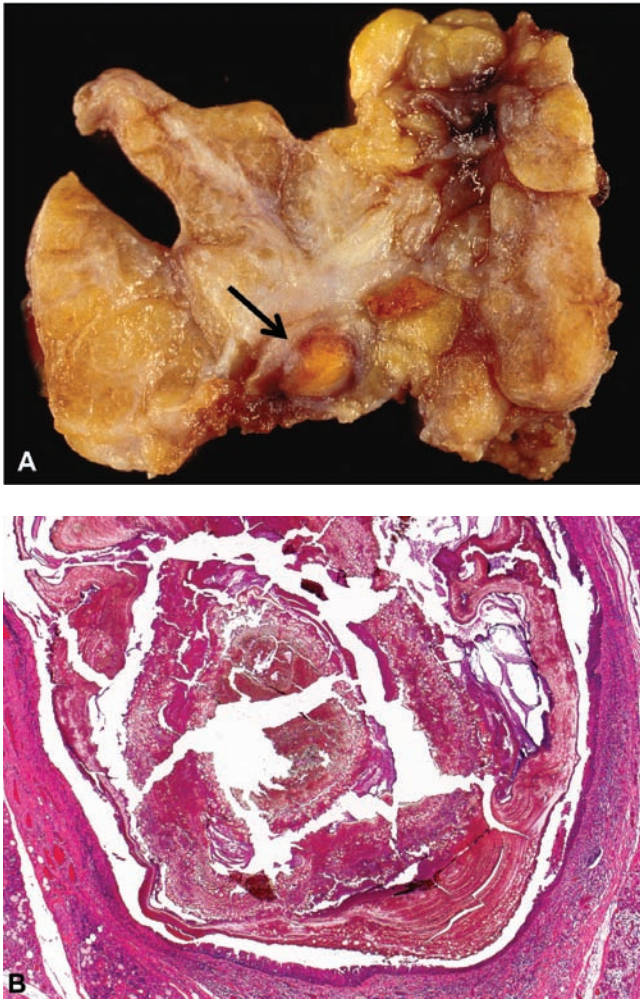


Figure 20 Sialolithiasis. (A) Duct near the hilum of the submandibular gland contains yellow-tan sialolith (arrow). (B) Sialolith consists of concentric laminations of calcification.

leading to inspissated secretion in the ducts. Seifert and Donath have suggested that a disorder of secretion causes changes in the electrolyte content resulting in increased viscosity of salivary secretions (5). Monoclonal and oligoclonal cytotoxic T-cell populations found in the affected salivary gland of patients with chronic sclerosing sialadenitis may suggest immune-mediated reactions against the ductal system (6).

On the other hand, recently it has become increasingly recognized that chronic sclerosing sialadenitis belongs to the group of immunoglobulin G4 (IgG4)-related sclerosing (systemic/autoimmune) diseases (7–11). This notion is further supported by the fact that chronic sclerosing sialadenitis has been associated with one or more extrasalivary IgG4-related sclerosing diseases, which are characterized by a chronic inflammatory cell infiltrate containing abundant IgG4-positive plasma cells, accompanied by atrophy of the normal parenchyma and sclerosis. Such

IgG4-related sclerosing diseases include sclerosing pancreatitis, also called autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, sclerosing mediastinitis, and tubulointerstitial nephritis. The close association suggests that at least some cases of chronic sclerosing sialadenitis share a common pathogenesis with other sclerosing diseases involving disturbance of IgG4 as a systemic disorder.

Clinical features. Chronic sclerosing sialadenitis can occur at any age between 12 and 83 years, but most patients are in the third-to-seventh decades with a mean age of 42 to 44 years (2,4). Some investigators have reported a slightly higher incidence in males, whereas others have reported a slight female predominance (2). Clinically, the patients typically present with a firm swelling of the submandibular gland with or without recurrent pain associated with eating. This presentation of an enlarging, firm growth can lead to the erroneous clinical diagnosis of a salivary gland neoplasm, particularly carcinoma. Duration of symptoms before patients receive treatment is highly variable. The glandular involvement is usually unilateral, but it can be bilateral. Cases with swelling of bilateral submandibular glands and lacrimal glands, similar to Mikulicz's disease, have been reported (12). As mentioned above, chronic sclerosing sialadenitis is sometimes associated with the extrasalivary IgG4-related sclerosing diseases; therefore, a systemic examination is recommended for patients with chronic sclerosing sialadenitis.

The serum concentrations of IgG4 in patients with chronic sclerosing sialadenitis are typically elevated (7). Autoantibodies specific for Ro (SS-A) and La (SS-B) associated with Sjögren's syndrome are usually negative. The involved submandibular gland is often removed for the purpose of diagnosis and/or treatment, while there have been several reports of chronic sclerosing sialadenitis responding well to corticosteroid therapy. Chronic sclerosing sialadenitis itself is an entirely benign inflammatory process, and no additional measures are warranted after removal, but a case of extranodal marginal zone B-cell lymphoma [mucosa-associated lymphoid tissue (MALT) lymphoma] in the setting of chronic inflammation in chronic sclerosing sialadenitis has been reported (13).

Pathology. Grossly, the involved glands are enlarged and firm but maintain their configuration. Histologically, chronic sclerosing sialadenitis is characterized by dense periductal lymphoplasmacytic infiltrate with lymphoid follicle formation, prominent fibrosis, and irregular ectasis of the ducts accompanied by inspissated secretion (Figs. 21, 22). The histopathologic features are quite variable depending on the degree of inflammation, fibrosis, and parenchymal involvement and are also different from case to case and from lobule to lobule within the same gland. The lobular architecture is usually preserved, but in the advanced stage, it is distorted and disrupted by prominent fibrosis and parenchymal destruction or atrophy. Ductal hyperplasia often occurs with periductal fibrosis and proliferation of lamellar collagen fibers whorled around the ducts in an onionskin

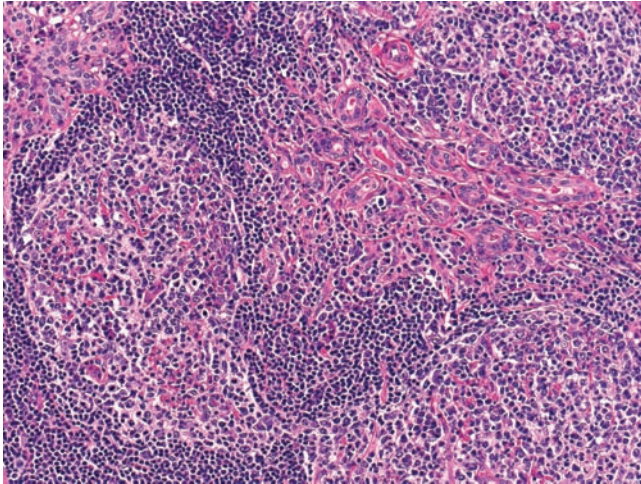


Figure 21 Chronic sclerosing sialadenitis (Küttner tumor) of the submandibular gland. Prominent lymphoid infiltration accompanied by well-developed lymphoid follicle formation and marked parenchymal loss.

arrangement. Sialolith and/or inspissated secretion within ducts are observed in some cases. Small clusters of epithelioid cells and isolated Langhans-type giant cells may be present, and occasionally these areas of granulomatous inflammation are conspicuous (14). Obliterative phlebitis, with vein occlusion caused by inflammatory infiltration and fibrosis, may also be identified (7).

According to Seifert and Donath, the severity of inflammation and fibrosis covers a spectrum that evolves through the following four stages (5,15):

- Stage 1: Focal chronic inflammation with periductal nests of lymphocytic infiltrate and moderately dilated ducts containing inspissated secretion.
- Stage 2: More marked diffuse lymphocytic infiltration and more severe periductal fibrosis. Duct system exhibits inspissated secretion and focal metaplasia with proliferation of ductal epithelium. Periductal lymphoid follicles are well developed. There is fibrosis in the centers of the lobules and atrophy of acini.
- Stage 3: Even more prominent lymphocytic infiltration, with lymph follicle formation with reactive germinal centers, reduction of the secretory gland parenchyma, periductal fibrosis with hyalinization, and ductal proliferation (Fig. 21). Squamous and goblet cell metaplasia in the ductal system may be present.
- Stage 4 (end stage): Destruction of the lobular architecture with marked parenchymal loss and sclerosis, described as salivary gland cirrhosis (the "burnt out" phase) (Fig. 22). Sometimes epimyoeipithelial islands can be observed.

The frequency of each stage based on more than 1000 cases in the Salivary Gland Registry at the

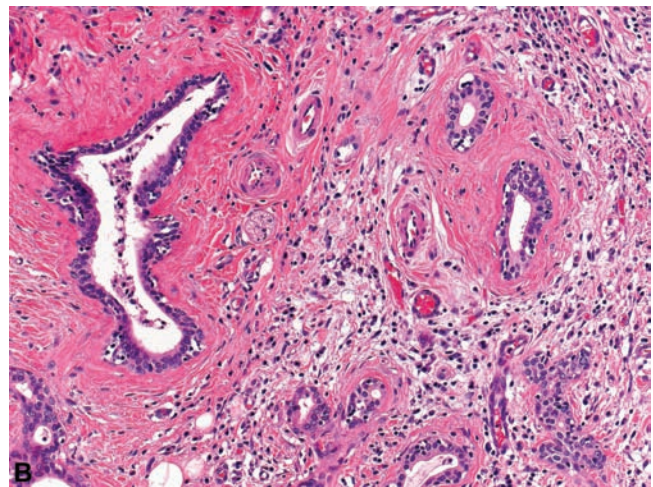
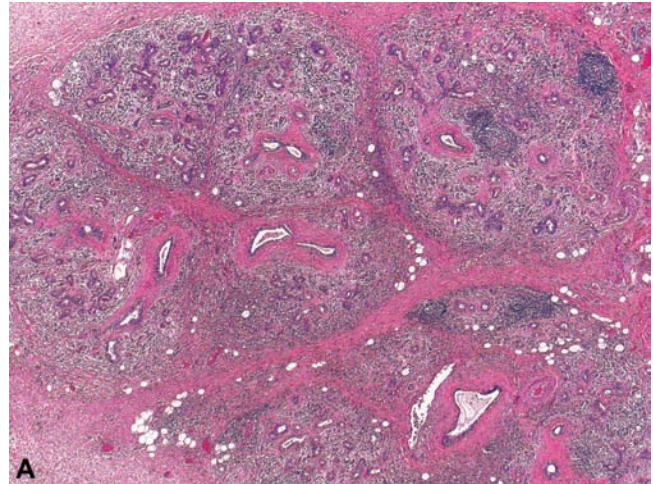


Figure 22 Chronic sclerosing sialadenitis (Küttner tumor), end-stage, of the submandibular gland. (A) Marked parenchymal loss, septal fibrosis, and moderate degree of lymphoid infiltrate. (B) There is periductal fibrosis accompanied by complete acinar loss and mild lymphoid infiltrate.

University of Hamburg, Germany, is as follows: Stage 1: 40%; Stage 2: 18%; Stage 3: 33%; Stage 4: 9% (15).

Immunohistochemically, abundant cytotoxic T cells are found, especially in close association with ducts and acini (6). The B-cell population is less pronounced and largely restricted to lymph follicles. Marked infiltration of IgG4-positive plasma cells is detected within the lesions (Fig. 23). Recently, Kitagawa et al. reported that the proportion of IgG4/IgG-positive plasma cells in chronic sclerosing sialadenitis cases ranged from 45.8% to 92%, whereas the percentage in cases of sialolithiasis and Sjögren syndrome was 0% to 4.9% (7).

Differential diagnosis. Chronic sclerosing sialadenitis should be differentiated from obstructive sialadenitis due to primary sialolithiasis, lymphoepithelial sialadenitis (LESA) ("benign lymphoepithelial lesion"),

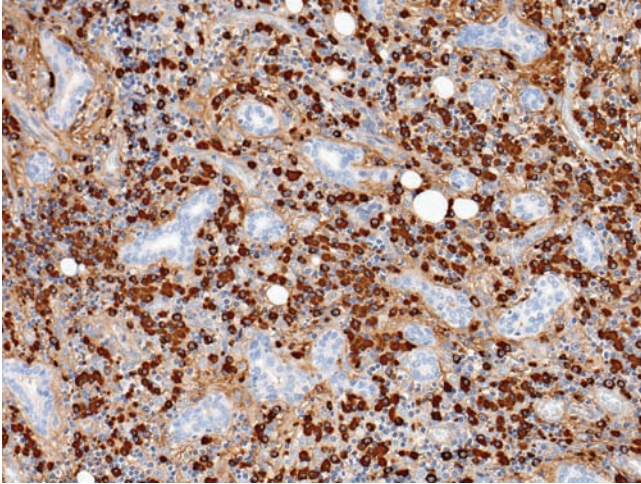


Figure 23 Chronic sclerosing sialadenitis (Küttner tumor) of the submandibular gland. Immunohistochemistry. Many IgG4-positive plasma cells are seen within the lesion.

Kimura's disease, malignant lymphoma including extranodal marginal zone B-cell lymphoma (MALT lymphoma), sclerosing variant of follicular lymphoma, and inflammatory pseudotumor (inflammatory myofibroblastic tumor) (2).

Obstructive sialadenitis due to primary sialolithiasis exhibits more prominent ductal ectasia and less evident lymphocytic infiltrate and fibrosis than chronic sclerosing sialadenitis. Lymphoepithelial islands ("epimyoepithelial islands") characteristic of LESA (benign lymphoepithelial lesion) are scarce or absent in chronic sclerosing sialadenitis. In addition, chronic sclerosing sialadenitis is typically much more fibrous than LESA. Furthermore, obstructive sialadenitis and LESA lack the feature of abundant IgG4-positive plasma cells seen in chronic sclerosing sialadenitis. Eosinophilic infiltration can be present in chronic sclerosing sialadenitis, but it is much less common than in Kimura's disease.

Chronic sclerosing sialadenitis is distinguished from extranodal marginal zone B-cell lymphoma (MALT lymphoma) by the absence of true lymphoepithelial lesions permeated by monocytoid B cells and the polytypic nature of lymphocytes proved by means of immunohistochemistry and polymerase chain reaction (16). Follicular lymphoma can also histologically mimic chronic sclerosing sialadenitis, especially its sclerosing variant. Unlike chronic sclerosing sialadenitis, however, follicular lymphoma contains a monoclonal tumor population with CD10-positive and bcl-6-positive immunophenotypes (17).

Both chronic sclerosing sialadenitis and inflammatory pseudotumor possess extensive fibrosis with chronic inflammatory cell infiltration. However, inflammatory pseudotumor forms a discrete mass with proliferation of myofibroblastic cells and lacks a lobulated architecture.

Radiation Sialadenitis

Radiotherapy is the most commonly used modality for treatment of the head and neck cancers (1). When the major salivary glands are included within the fields of radiotherapy, many patients develop swelling and tenderness of the irradiated glands as well as elevation of the serum amylase level within hours of receiving even the first treatment in a course of fractionated radiotherapy. These symptoms may be transient, but a significant proportion of the patients will suffer persistent salivary gland dysfunction, resulting in xerostomia accompanied by a variety of complications, such as dysphagia, abnormal taste sensations, oral mucositis, dental caries, and periodontal disease (2). These complaints may persist as a long-term consequence of the radiation damage to the salivary glands, even after cessation of radiotherapy. In addition to the reduction in quantity, the composition of the secreted saliva also changes because of the influence of radiotherapy. Saliva secreted from irradiated salivary glands has a lower pH, lower protein and secretory antibody contents, higher salinity, and increased numbers of cariogenic microorganisms (3). The severity of salivary gland damage and dysfunction depends on the dose and the duration of irradiation.

The important pathogenetic factor of radiation sialadenitis is the direct irradiation effect on the salivary gland tissue rather than the result of radiation-induced changes in the vasculature (4). Serous acinar tissue of the parotid gland is considerably more radiosensitive than mucous glandular tissue of the submandibular gland (5). The radiosensitivity of the acinar cells depends on the content of secretory granules, which contain a large amount of heavy metals limited by the membrane (6). Released heavy metals as a result of the irradiation may cause membrane lipid peroxidation by means of a redox system, thus enhancing the process of apoptotic cellular death (6).

Generally, the acute alterations progress to a chronic stage, with depletion of acinar structures, and resulting interlobular and periductal fibrosis and chronic inflammatory cellular infiltrate. It has been suggested that the histologic changes in the irradiated salivary glands can be divided into three stages according to the degree of severity of the inflammatory process and the destruction of gland structure (7). These correlate closely with the clinical symptoms and the outcome of late radiation-induced sequelae (7).

Stage I is characterized by marked swelling and vacuolization of the serous glandular acinar cells with a reduction of secretory granules. However, mucous glands may manifest few histologic changes. There is also moderate atrophy of isolated glandular acini with a scant lymphocytic infiltration and moderate fibrosis. Stage I corresponds to an acute response to relatively low-level irradiation that lasts only several days.

In Stage II, significant atrophy of the glandular acini is accompanied by ectasia of the excretory ducts filled with secretion. Goblet cell and squamous cell

metaplasia may be seen focally in the ductal epithelium. Moderate periductal fibrosis and significant lymphocytic infiltration are usually also present. Interstitial lipomatosis may develop in some areas. Stage II corresponds to changes observed after higher irradiation doses in experimental studies. The resultant changes are no longer completely reversible and cause functional loss of the glandular tissue.

Stage III is characterized by marked parenchymal loss with destruction of the lobular structure, extensive lymphocytic infiltration, interstitial fibrosis, and ductal ectasia with intraluminal accumulation of secretions (Fig. 24A). Metaplastic changes of the ductal epithelium may be prominent, sometimes together with cellular atypia (Fig. 24B), and may potentially be difficult to distinguish from squamous cell carcinoma

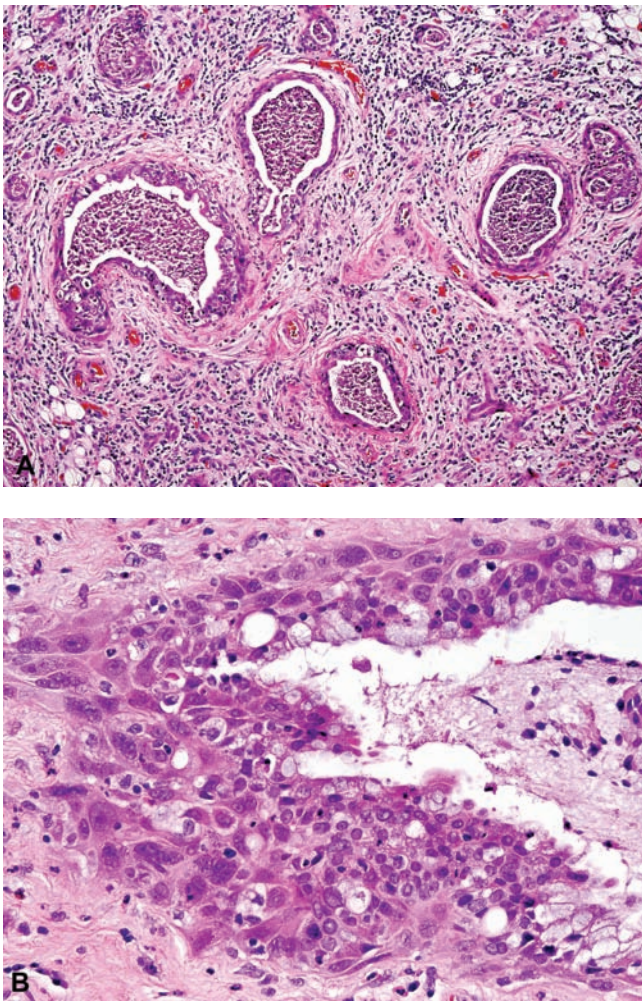


Figure 24 Radiation sialadenitis of the submandibular gland. (A) Marked parenchymal loss with destruction of the lobular structure, interstitial fibrosis, lymphocytic infiltration, and ductal ectasia with intraluminal accumulation of secretions containing cell debris are evident. (B) Prominent squamous and goblet cell metaplasia of the ductal epithelium, together with cellular atypia. Source: Courtesy of Dr. Jean E. Lewis, Mayo Clinic, Rochester, Minnesota, U.S.A.

or mucoepidermoid carcinoma. These histologic features are observed most frequently after more than three months of irradiation and after high irradiation doses. The resultant changes are completely irreversible and are associated with permanent damage and impaired glandular secretory function.

On immunohistochemistry, a loss of amylase reaction and an increasing expression of lysozyme, lactoferrin, and secretory component may be observed in the salivary ducts (7). The great majority of periacinar lymphocytic infiltrates are CD8-positive cytotoxic T cells associated with acinar cell destruction (8).

Cheilitis Glandularis

Introduction. Cheilitis glandularis is a rare inflammatory disease affecting the minor salivary glands of the lip that was first described by von Volkman in 1870 (1). He described a suppurative chronic inflammatory condition of the lower lip characterized by mucopurulent discharge through the ductal orifices of the labial minor salivary glands.

Cheilitis glandularis is a poorly understood entity, and its etiology is still unknown, but various predisposing factors have been suggested, including genetic predisposition (autosomal dominant pattern of inheritance), chronic exposure to sunlight and wind, smoking, poor oral hygiene, mouth breathing, trauma (habitual lip licking), and a compromised immune system human immunodeficiency virus (HIV) infection (2–11).

Clinical features. The condition is seen most frequently in adult men between the fourth and seventh decades. However, a few cases have been reported in women and children. It is most commonly seen in the lower lip, although it has also been reported in the upper lip and the palate. When the lesion extends to the buccal mucosa, the term “suppurative stomatitis glandularis” may be applied (12,13).

According to the clinical stages of progression of the disease, cheilitis glandularis has historically been subclassified into three types: simple, superficial suppurative, and deep suppurative (8). Each subtype represents part of a continuous spectrum of the same disease category wherein, in the simple type, the disease may progress from the superficial to the deep suppurative types. The simple type is described as multiple, painless, papular surface lesions with central depressions and red or black puncta. The lesions may extrude clear mucinous material upon manipulation. The superficial suppurative type, also referred to as Baelz’s disease, presents as multiple, painless, indurated swellings of the lip with ulceration and crust formation. Digital palpation of the lip will produce clear-to-cloudy fluid from the ductal orifices. The deep suppurative type, also called cheilitis glandularis apostematosa, cheilitis glandularis suppurative profunda, or myxadenitis labialis, demonstrates a deep-seated infection accompanied by formation of abscesses, sinus tracts and fistulae, and scarring, resulting in nodular enlargement of the lip. Viscous secretion and mucopurulent material may spontaneously exude onto the mucosal surface.

Cheilitis glandularis, especially its deep suppurative type, has been closely associated with the development of squamous cell carcinoma. The incidence of malignant transformation of cheilitis glandularis has been reported to range from 18% to 35% (3).

Pathology. Incisional biopsy consisting of surface epithelium and an adequate amount of minor salivary glands is often recommended to establish a definitive diagnosis and to rule out other specific granulomatous diseases, actinic cheilitis, or carcinoma. The histologic features of cheilitis glandularis have been described as nonspecific inflammation of minor salivary gland tissue with broad variations. The histologic changes can include ductal ectasia or hyperplasia with or without squamous metaplasia, atrophy or distention of acini, periductal acute and chronic inflammatory infiltration, and interstitial fibrosis. Suppuration and sinus tracts may be present in cases that involve bacterial infection. Oncocytic metaplasia and mucous cell metaplasia of the duct epithelium may be observed and are sometimes prominent. Oncocytic metaplasia with papillary projections can be confused with oncocytic variant of papillary cystadenoma (11). Other histologic findings include surface hyperkeratosis, erosion, or ulceration.

Treatment of cheilitis glandularis ranges from a preventive approach to surgical intervention. Reduction or elimination of predisposing factors is the first step in management. Conservative treatment includes the usage of topical or intralesional corticosteroids combined with antibiotic therapy. Patients with the deep suppurative type of cheilitis glandularis should be considered for surgical excision because of the high risk of developing squamous cell carcinoma. Recurrence after surgery is rare.

Necrotizing Sialometaplasia

Introduction. Necrotizing sialometaplasia is a benign, self-limiting, reactive inflammatory condition of the salivary glands. It was first reported as a distinct clinicopathologic entity of the minor salivary gland of the hard palate by Abrams et al. in 1973 (1). Since the clinical and histopathologic features of necrotizing sialometaplasia often simulate those of malignancies, including squamous cell carcinoma and mucoepidermoid carcinoma, the report of Abrams et al. and subsequent reports have emphasized the importance of its correct diagnosis (1–6). Familiarity with this disease can avoid misdiagnosis and inappropriate treatment. Ischemia caused by the impairment of the vasculature supplying the salivary gland tissue has been implicated as the most likely etiology for necrotizing sialometaplasia by both clinical and experimental evidence (7,8), but the predisposing cause is unclear in many cases. The factors believed to lead to ischemia include traumatic injury, administration of local anesthetics, smoking, alcohol consumption, radiation, infection, intubation, and surgical procedures (3). Necrotizing sialometaplasia has also been described in a patient with embolization from carotid endarterectomy, Buerger's disease, or Raynaud phenomenon, supporting this pathogenic mechanism (9).

In an experimental study using a rat model, local anesthetic injections and ligation of the arteries induced histologic changes similar to those of necrotizing sialometaplasia (8).

Clinical features. Necrotizing sialometaplasia is a rare disorder, involving an estimated 0.3% of all biopsied lesions from the oral cavity (2). Most cases occur in the intraoral minor salivary glands, especially the palate (77.2% of the cases) (3). Other salivary gland sites include the minor glands of the lower lip, retromolar pad area, tongue and buccal mucosa (9.8%), and the major salivary glands (8.7%) (10), particularly the parotid. Necrotizing sialometaplasia has also rarely been reported in the extrasalivary seromucinous glands of the nasal cavity, nasopharynx, paranasal sinuses, larynx, and trachea (3). Similar lesions have been recognized in the skin, breast, and lung (11–13). The average age of the patients with necrotizing sialometaplasia is 45.9 years, with a range of 1.5 to 83 years (3). There is a male preponderance; the male-to-female ratio being approximately 2:1 (3).

The typical clinical presentation is that of a deep, crater-like ulcer of the palate that resembles a malignant process. These ulcerated lesions range from 0.7 to 5.0 cm, with an average size of 1.8 cm (3). Palatal lesions are usually unilateral, but bilateral synchronous lesions and metachronous lesions can occur. Some lesions of necrotizing sialometaplasia may present as a submucosal swelling, without ulceration of the overlying mucosa. Patients with necrotizing sialometaplasia often complain of pain (63% of patients) or numbness (13%) (3). Erosion of the palatal bone may occur in both ulcerated and nonulcerated lesions. The average duration of the symptoms is three weeks with an upper range of up to six months. Most cases of necrotizing sialometaplasia appear to arise spontaneously, whereas others are associated with a history of trauma, vomiting, radiation therapy, surgery, inflammatory disease, and either benign or malignant neoplasms.

The suggested evolution of the lesions of necrotizing sialometaplasia includes five stages: infarction, sequestration, ulceration, reparation, and eventual healing (14). The prognosis for necrotizing sialometaplasia is excellent and spontaneous complete healing occurs within 3 to 12 weeks, with an average healing time of approximately five weeks, depending on the size of the lesion and the presence or absence of bony perforation. No specific treatment is necessary, but biopsy of the lesion may be required to establish a correct diagnosis.

Pathology. The principal histologic features of necrotizing sialometaplasia are described as follows: (i) lobular infarction or necrosis of salivary gland tissue, (ii) simultaneous squamous metaplasia of ducts and acini, (iii) bland-appearing nuclear morphology of squamous cells, (iv) prominent granulation tissue and inflammatory components, and (v) maintenance of the general lobular architecture in spite of fairly extensive inflammatory and metaplastic changes, often involving more than one lobule (1) (Fig. 25). The last feature is most helpful in distinguishing necrotizing sialometaplasia from a malignant

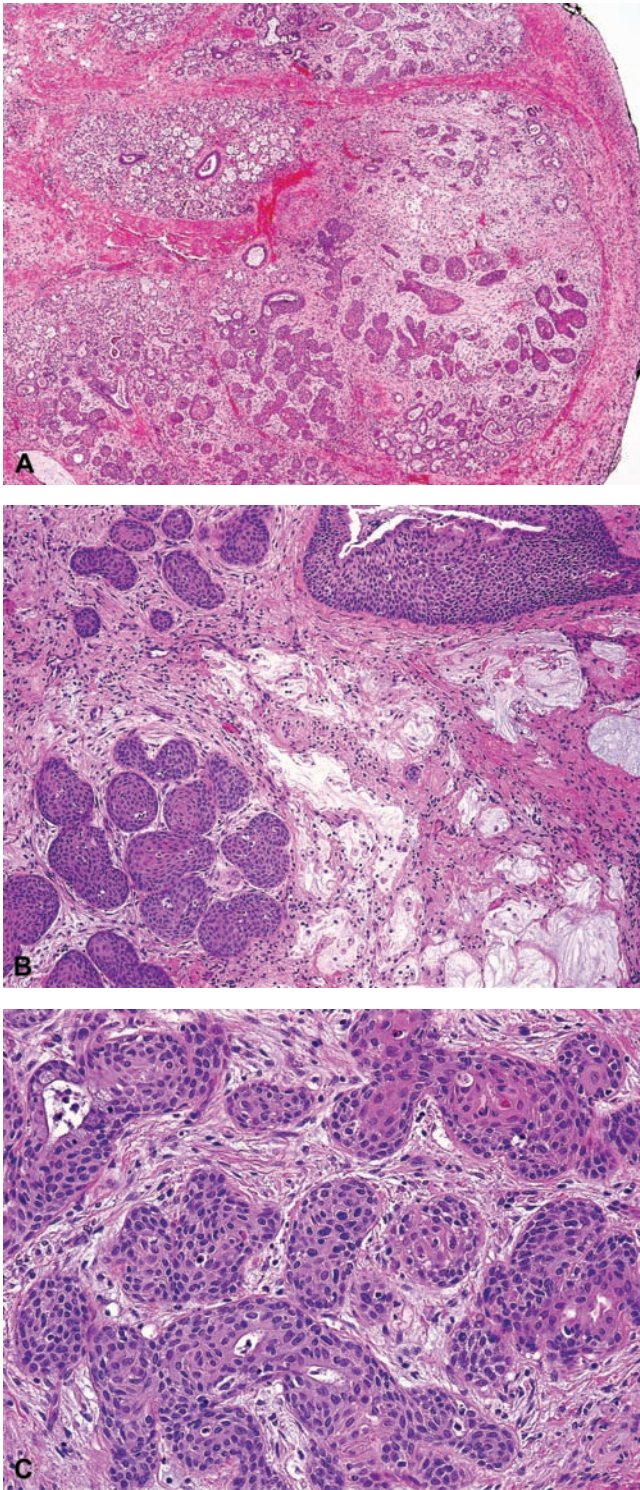


Figure 25 Necrotizing sialometaplasia. (A) Low-magnification view shows that a palatal lesion is composed of a mixture of necrotic and metaplastic lobules. Note the maintenance of the general lobular architecture. (B) Squamous metaplasia of the ducts and acinar necrosis with mucin pooling are evident. (C) Metaplastic squamous nests with remaining ductal luminal structures and a few mucous cells. The outline of the nests is smooth, and squamous cells have no significant cellular atypia. Source: Courtesy of Dr. Jean E. Lewis, Mayo Clinic, Rochester, Minnesota, U.S.A.

process, but may be of little benefit if submitted surgical material is scanty.

At low magnification, the lesion is composed of a mixture of necrotic and metaplastic lobules (Fig. 25A). There is a spectrum of histologic findings in necrotizing sialometaplasia depending on the duration of the lesion, ranging from a dominant feature of complete or partial coagulative necrosis of the acini, with minimal or almost no inflammation in the early stages to extensive squamous metaplasia of the ducts and reactive fibrosis with edema and marked inflammation being predominant in the late stage. Thus, although necrosis is a defining hallmark of necrotizing sialometaplasia, it may not always be seen in the biopsy. Mucous escape reaction and mucin pooling may be present within the areas of necrosis and granulation tissue (Fig. 25B). The inflammatory infiltrate consists mainly of neutrophils and foamy macrophages and, less commonly, of lymphocytes, plasma cells, and eosinophils. On the other hand, squamous metaplasia of the ducts and acini is a consistent finding in necrotizing sialometaplasia. The outline of the metaplastic squamous nests is generally smooth, and they are distributed within the lobular architecture (Fig. 25C). Ductal luminal structures and mucous cells can remain and be enclosed within the solid squamous nests. Squamous cells usually have no significant cellular atypia, but in some parts, the nests may be predominantly composed of basaloid cells with hyperchromatic nuclei or exhibit reactive atypia with a high rate of mitosis. In minor salivary gland or seromucinous gland sites, pseudoepitheliomatous hyperplasia of the surface epithelium overlying the lesion or adjacent to the ulcer is commonly present.

Differential diagnosis. The main differential diagnoses of necrotizing sialometaplasia are squamous cell carcinoma and mucoepidermoid carcinoma. The distinction is important to avoid unnecessary radical surgery. Florid pseudoepitheliomatous hyperplasia of the overlying mucosa and squamous metaplasia can be misinterpreted as squamous cell carcinoma, while the presence of residual mucous cells entrapped within the squamous nests may be confused with mucoepidermoid carcinoma.

Necrotizing sialometaplasia is distinguished from these malignant processes by the recognition of the maintenance of the lobular architecture, absence of infiltrative growth pattern, presence of lobular infarctive necrosis, lack of frankly malignant cytology, and the evidence of residual ductal lumina. In a small biopsy specimen, however, the differential diagnosis is often problematic because the lobular pattern may not be apparent. Therefore, an adequate amount of biopsy material is required to ensure a correct diagnosis. Identification of myoepithelial cells surrounding squamous nests by immunostaining for calponin and/or smooth muscle actin may help to distinguish necrotizing sialometaplasia from squamous cell carcinoma and mucoepidermoid carcinoma (6). In addition, necrotizing sialometaplasia lacks the intermediate cells and cystic structures of mucoepidermoid carcinoma.

Another lesion of the minor salivary glands that should be considered for the differential diagnosis is subacute necrotizing sialadenitis, which is a rare

Table 1 Comparison of Clinicopathologic Features Between Necrotizing Sialometaplasia and Subacute Necrotizing Sialadenitis

	Necrotizing sialometaplasia	Subacute necrotizing sialadenitis
Clinical features:		
- No. of cases	Approximately 200	31
- Age range (yr)	1.5–83 (mean, 45.9)	15–70 (mean, 26.7)
- Gender (M:F)	3:1	3:1
- Site	Palate: 142 Other locations: 58	Palate: 24 Other locations: 7
- Lesion size, cm	0.7–5.0	0.3–2.5
- Symptoms	67 of 200 cases had pain	Painful
- Appearance	Usually ulcerated	Nonulcerated
- Duration	4 days–3 mo (mean, 21 days)	1 day–1 wk
- Healing time /recurrence	Healing usually after excisional biopsy/none	3 wk/none
Pathologic features:		
- Surface ulcer	Deep ulcer	Absent
- Pseudoepitheliomatous hyperplasia	Usually present	Absent
- Necrosis/pattern	All stages/usually lobular	Early and moderate/focally acinar
- Ductal squamous metaplasia	Always present	Mild or absent
- Atrophy of ducts	Severe	Mild
- Inflammatory cells	Chronic	Mixed/subacute
- Eosinophils	Usually absent	Conspicuous

Source: From section "Necrotizing Sialometaplasia" Refs. 3 and 18.

self-limiting inflammatory condition characterized by a diffuse inflammatory infiltrate and acinar necrosis similar to necrotizing sialometaplasia, but without squamous metaplasia of the salivary ducts (15). The relationship between subacute necrotizing sialadenitis and necrotizing sialometaplasia is still under discussion (16). The clinicopathologic features of these entities are summarized in Table 1 (17,18).

Subacute Necrotizing Sialadenitis

Introduction. Subacute necrotizing sialadenitis is a rare, self-limiting, nonspecific inflammatory condition of the intraoral minor salivary glands. It was first described by Werning et al. in 1990 (1), and there have been 31 cases reported to date (1–6). Although there are considerable clinical and histologic differences between the two conditions (Table 1) (3,6), it remains controversial whether subacute necrotizing sialadenitis is a distinct, specific entity, or whether it belongs to the spectrum of necrotizing sialometaplasia (5). Even if the latter is the case, subacute necrotizing sialadenitis and early lesions of necrotizing sialometaplasia share some common histologic features, suggesting a possible relationship between them (5). The exact etiology of subacute necrotizing sialadenitis has not been defined, but an infectious process or immune responses to an unknown allergen have been postulated (1,3).

Clinical features. The age of the patients ranges between 15 and 70 years, with a mean age of 26.7 years and the majority of cases occurring in the second and third decades (6). Subacute necrotizing sialadenitis shows a male predominance with male-to-female ratio of 3:1 (6). These epidemiologic descriptions might have a case selection bias since a significant number of the reported patients belonged to a military population (1,3). Many patients with subacute necrotizing sialadenitis in previous reports shared close living quarters such as military barracks, and

there was an association with upper respiratory tract infection, with a peak incidence in the fall and winter seasons. The palate, particularly the hard palate, is most commonly involved, as in the case of necrotizing sialometaplasia (6). Other sites of occurrence include the tonsillar area, buccal mucosa, ventral surface of the tongue, and the upper lip. Clinically, the lesion typically presents as a nonulcerated, erythematous, nodular swelling accompanied by an abrupt onset of pain. The size ranges from 0.3 to 2.5 cm. The duration of the symptoms before diagnosis is usually less than a week. The lesions generally heal within two to three weeks after incisional or excisional biopsy, without any additional medications. Clinical differences between subacute necrotizing sialadenitis and necrotizing sialometaplasia include age distribution, presence or absence of pain and ulceration, length of duration, and healing time (Table 1) (3,6).

Pathology. Histologically, subacute necrotizing sialadenitis is characterized by marked acute and chronic inflammatory cell infiltration accompanied by focal necrosis and loss of acinar cells (Fig. 26). The inflammatory infiltrate is composed of neutrophils, lymphocytes, histiocytes, and eosinophils. Eosinophils are sometimes a predominant element. The inflammation may appear to be the earliest event, occurring before the development of acinar necrosis. Acinar necrosis is identified in only a part of the lesion, and the lobular-type acinar necrosis, typical of necrotizing sialometaplasia, is not seen. Residual ducts may show slight atrophy and mild dilatation. Acinar and/or ductal squamous metaplasia, a defining criterion of necrotizing sialometaplasia, is not the feature of subacute necrotizing sialadenitis. No significant fibrosis is observed. There is no pseudoepitheliomatous hyperplasia of the overlying mucosal epithelium. Ultrastructurally, electron-dense, virus-like particles have been reported in some cases of subacute necrotizing sialadenitis (1).

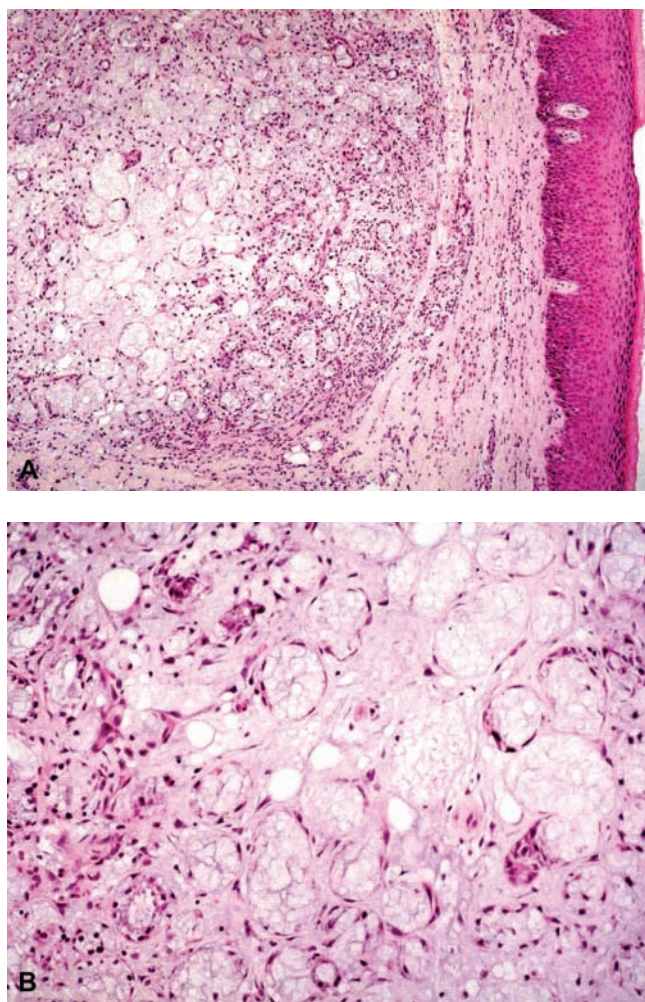


Figure 26 Subacute necrotizing sialadenitis of the palate. (A) Low-power view shows focal acinar necrosis with an inflammatory cell infiltration. Note the lack of acinar and/or ductal squamous metaplasia. (B) High magnification reveals the evidence of focal necrosis of acinar cells.

Recurrent Parotitis

Introduction. Recurrent parotitis is a well-recognized entity in children, characterized by recurring episodes of swelling of the parotid gland. Although it is relatively rare, it is still the second most common inflammatory salivary gland disease in children, next to mumps (1–3). Recurrent parotitis is generally associated with nonobstructive sialectasis of the parotid gland. Although a number of etiologies have been suggested, the exact causative factor of the disease has yet to be determined. Candidates include congenital sialectasis of the salivary duct, genetic inheritance, viral or bacterial infection, allergy, and a local manifestation of an autoimmune disease (1–3). The most probable theory is a combination of a congenital malformation of portions of the salivary ducts and

infections ascending from the mouth after dehydration of the affected children, which provides a ground for bacterial infection (1,2). However, the sialectasis may be both the cause and the result of the recurrent exacerbations of the parotitis (4).

Clinical features. The age of onset of recurrent parotitis has been reported to be between 3 months and 16 years, but it mostly starts between three and six years with a peak during the first year of school (1). There is a male predilection. Recurrent parotitis presents as an intermittent, painful swelling of either unilateral or bilateral parotid glands during mastication and/or swallowing, generally accompanied by fever and malaise. The disease is often clinically misdiagnosed initially as mumps. The number of attacks varies individually, but most commonly occurs every three to four months (1–3). The swelling lasts from several days to two weeks, and typically resolves spontaneously, regardless of the treatment. Between the episodes, the patient is free from symptoms. Recurrent parotitis is generally self-limiting, and after puberty, by age between 10 and 15 years, the exacerbations usually subside and may disappear completely, but there are persistent cases (2). Although it usually is not accompanied by purulent secretion, the majority of affected glands grow bacteria on culture of saliva.

Sialography has been considered the most important and accurate diagnostic tool, though its role is now becoming secondary to ultrasonography (5). The typical changes in recurrent parotitis on sialogram are punctate and globular sialectasis, measuring 1 to 2 mm in diameter, scattered throughout the gland. Ultrasonographic examination shows multiple small hypoechogenic areas, corresponding to the punctate sialectases demonstrated by sialography. These changes are usually bilateral, even if the clinical manifestations are unilateral. These abnormalities tend to diminish and sometimes disappear after the disease becomes quiescent, but they may persist even after all other symptoms have resolved.

Pathology. The histologic findings of recurrent parotitis are characterized by cystic dilation of interlobular ducts accompanied by massive periductal lymphocytic infiltration (Fig. 27) (1). The dilated ducts correspond to the sialectases seen on sialograms, and there seems to be no element of obstruction in most cases. The lymphocyte infiltrate usually contains well-formed lymphoid follicles. The ductal epithelium is commonly hyperplastic and metaplastic and is often permeated by lymphocytes. Some investigators proposed that this lymphocytic infiltration damages the duct wall reticulum, allowing extravasation of secretions into the gland parenchyma, thus exacerbating the inflammation (6). In the later stage of the disease, there may be various degrees of atrophy of the acini with interstitial fibrosis. Resolution of symptoms with age may be due to regeneration of glandular elements.

The main treatments of an acute phase of recurrent parotitis are either conservative observation or antibiotic treatment. Penicillin V is a good choice for acute infections. Performing sialography itself may

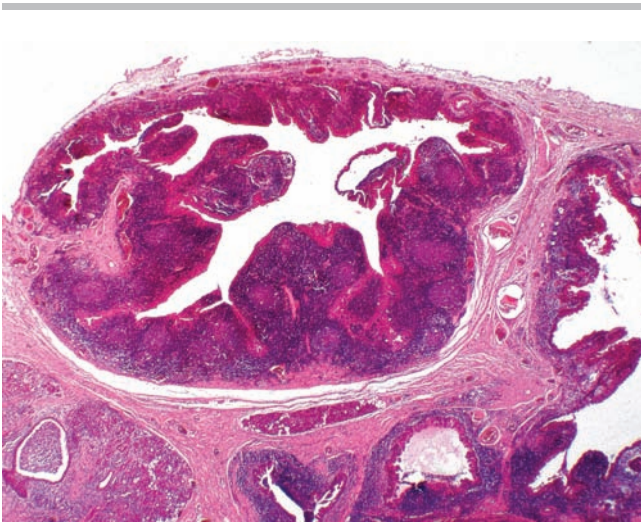


Figure 27 Juvenile recurrent parotitis. Low-power view demonstrates cystic dilation of interlobular ducts accompanied by massive periductal lymphocytic infiltration with well-formed lymphoid follicles.

be useful in improving the symptoms. No preventive therapy against recurrent parotitis is available. Other treatments are much more invasive when applied to the adults with persistent severe disease, including duct ligation, parotidectomy, and tympanic neurectomy.

Viral Sialadenitis Including Mumps, Cytomegalovirus, and HIV-Associated Lymphoepithelial Cyst

Viral infections involving the salivary glands are more common than those of bacterial origin. Viral sialadenitis is a manifestation of a systemic infection, and the salivary glands are affected by a hematogenous spread of virus rather than direct infection to the organ as in bacterial sialadenitis. A variety of viruses are known as causative agents of sialadenitis, including the paramyxovirus (mumps), cytomegalovirus, HIV, coxsackie A virus, Epstein-Barr virus (EBV), echovirus, herpes virus, lymphocytic choriomeningitis virus, adenovirus, and influenza A and parainfluenza viruses (1). A comprehensive discussion of all cases of these viral-associated sialadenitis is beyond the scope of this chapter; however, several diseases that merit mention in this context are mumps (2), cytomegalovirus (3), and HIV-associated lymphoepithelial cysts (4–10).

Mumps. Mumps is by far the most common cause of parotid swelling and is the most common viral agent involving the salivary glands (2). Mumps is caused by a highly contagious paramyxovirus that is transmitted by saliva droplets or direct contact with articles that have been contaminated with infected saliva. A vaccine made from attenuated live mumps virus has reduced the frequency. Before the development of effective vaccination, mumps was a common childhood disease worldwide and is still a significant threat to health in developing countries. The peak

incidence is between the ages of four and six years, but the infection can be seen in other age groups. The incubation period is two to three weeks, with a clinical onset characterized by pain and swelling of one or both parotid glands. Systemic symptoms include fever, malaise, myalgia and headache, and usually resolve before the parotid swelling. While symptoms are generally not severe in children, adults infected with mumps are more likely to develop severe symptoms and complications. The diagnosis is usually made on clinical presentation. Demonstrating antibodies to the mumps S and V antigen by enzyme-linked immunosorbent assay can confirm the diagnosis. Some laboratories use molecular methods that are based on nested polymerase chain reaction.

Many cases are subclinical, and studies have shown that more than 95% of adults have neutralizing antibodies. Orchitis occurs in 10% to 20% of infected males, but it is usually unilateral, and sterility only rarely ensues; aseptic meningitis occurs in about 5% of those infected. In older people, the central nervous system, pancreas, prostate, breast, and other organs may be involved. Viral infections can cause severe degrees of sensorineural hearing loss in one ear, and sometimes in both, at any age. The disease is generally self-limiting, and the outcome is usually good. Swelling and other acute symptoms usually subside within two weeks. There is no specific treatment apart from controlling the symptoms with analgesics.

The opportunity for histologic examination of infected glands is exceedingly rare. The histologic features of the swollen parotid glands include diffuse interstitial edema, intense hyperemia, and a dense inflammatory infiltrate composed of histiocytes, lymphocytes, and plasma cells. This infiltrate may compress the salivary gland parenchyma resulting in acinar cell vacuolization and ductal dilatation.

Cytomegalovirus. Cytomegalovirus (from the Greek *cyto-*, “cell,” and *-mega-*, “large”) is a member of *Betaherpesvirinae* in the subfamily of *Herpesviridae*. Most people are infected with cytomegalovirus at some point in their life, although the age of infection varies worldwide. In developing countries, most infections are acquired during childhood, whereas, in developed countries, up to 50% of young adults are seronegative. Cytomegalovirus is not highly contagious, thus the infection requires close, intimate contact with a person excreting the virus in their saliva, urine, or other bodily fluids. Cytomegalovirus can be sexually transmitted and can also be transmitted via breast milk, transplanted organs, and, rarely, from blood transfusions. Diagnostic procedures include the enzyme-linked immunosorbent assay for measuring the antibody to cytomegalovirus.

Cytomegalovirus infection without symptoms is common in infants and young children. Clinically significant cytomegalovirus disease frequently develops in patients immunocompromised by HIV infection, organ transplantation, or bone-marrow transplantation (3). Symptomatic disease in immunocompromised individuals can affect almost every organ of the body, resulting in fever of unknown origin, pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis,

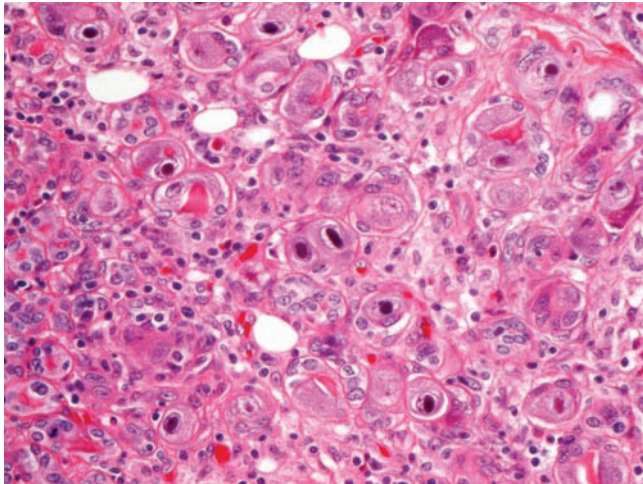


Figure 28 Cytomegalovirus infection. Several enlarged parotid gland duct cells exhibit intranuclear viral inclusion bodies.

and neuropathy. Cytomegalovirus infections are frequently associated with salivary glands, but significant clinical manifestations of cytomegalovirus-infected patients are usually seen in other organs. Cytomegalovirus infection is a major cause of death in immunocompromised patients.

Additionally, congenital transmission from a mother with acute infection during pregnancy is an important cause of a variety of abnormalities in newborns. Congenital cytomegalovirus infection is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, cytomegalovirus, and herpes simplex virus). The clinical syndrome of congenital cytomegalic inclusion disease includes jaundice, splenomegaly, thrombocytopenia, intrauterine growth retardation, microcephaly, and retinitis. No treatment is generally necessary for cytomegalovirus infection in the healthy individual since the majority of infections resolve spontaneously. Antiviral drug therapy is now being evaluated in infants.

The pathologic hallmark of cytomegalovirus infection in the salivary glands is an enlarged duct cell with characteristic intranuclear viral inclusion bodies (Fig. 28). The microscopic description given to these cells is most commonly an "owl's eye."

HIV-associated lymphoepithelial cyst
(HIV-salivary gland disease).

Introduction. HIV is currently the leading cause of death in Africa and the fourth leading cause of death worldwide. Cystic lymphoepithelial lesions of the salivary glands showing nodular or diffuse enlargements can occur in patients with HIV infection, with variable designations as HIV-associated lymphoepithelial cyst (LEC), HIV-salivary gland disease, benign lymphoepithelial lesion, cystic lymphoepithelial lesion, and diffuse infiltrative lymphocytosis syndrome (10). HIV-associated LEC and lymphoepithelial sialadenitis in Sjögren's syndrome share some common morphologic features. Lesions that morphologically resemble HIV-associated LEC are also

observed in HIV-negative patients (7). HIV-associated LEC may develop either from preexisting salivary gland inclusions in the intraparotid lymph nodes or from a secondary lymphocytic infiltration of the salivary gland parenchyma provoking LECs and lesions. A computer-assisted three-dimensional reconstruction study supports the latter hypothesis regarding its pathogenesis (6).

Clinical Features. About 1% to 10% of adult patients with HIV infection develop HIV-associated LEC (4,10). The age distribution of patients with HIV-associated LEC falls into two groups: children born to HIV-infected mothers and adults aged between 20 and 60 years, but most are in the 25- to 50-year age group. HIV-associated LEC has a distinct male predominance of nearly 7:1 (4). Patients have been intravenous drug users, homosexual males, transfusion recipients, and hemophiliacs. The lesion almost exclusively arises in the parotid gland, and the occurrence in the other salivary glands, including submandibular gland and minor salivary glands, is rare. Involvement may be unilateral but is most commonly bilateral. The main symptom is painless, slow-growing swellings of the affected glands with or without the manifestation of dry mouth. HIV-associated LEC usually develops early in the course of HIV infection and sometimes is the first clinical manifestation. Patients almost invariably have accompanying cervical lymphadenopathy. HIV-associated LEC is thought to reflect a localized form of persistent generalized lymphadenopathy. Fevers, fatigue, night sweats, diarrhea, or weight loss may also be present. Patients with HIV-associated LEC are negative for the serologic markers commonly present in Sjögren's syndrome, such as anti-SS-A and SS-B, antinuclear antibodies, or rheumatoid factor. HIV-associated LEC has a characteristic appearance on CT and MRI as well as ultrasonography, where the salivary swellings are recognized as multicentric cysts or larger cysts ranging from 0.5 to 4.0 cm in diameter (6).

Although the salivary gland swelling may fluctuate, they are generally persistent and long standing. Patients with HIV-associated LEC are at increased risk of developing aggressive B-cell lymphomas, most commonly of the Burkitt-type and diffuse large cell lymphoma. No definitive treatment has been established for HIV-associated LEC. The clinical progression of the salivary gland swelling may require surgical intervention for cosmetic reasons. Steroid, antiretroviral medications, and radiation therapy may reduce the size of the lesion. Therapy for the symptom of dry mouth is essential for the clinical control.

Pathology. Grossly, multiple cysts of variable diameters up to 5 cm can be seen usually in the superficial lobe of the parotid glands. The lobular architecture of the glands is preserved.

Histologically, the lesion is characterized by poorly circumscribed multinodular areas composed of multicystic structures surrounded by dense lymphoid infiltrates with florid lymphoid follicular hyperplasia and lymphoepithelial lesions (Fig. 29A). The cysts are lined predominantly by nonkeratinized stratified squamous epithelium and focally by cuboidal-type cells, permeated by mainly monocytoid and/or marginal zone B cells and also sparsely by T cells

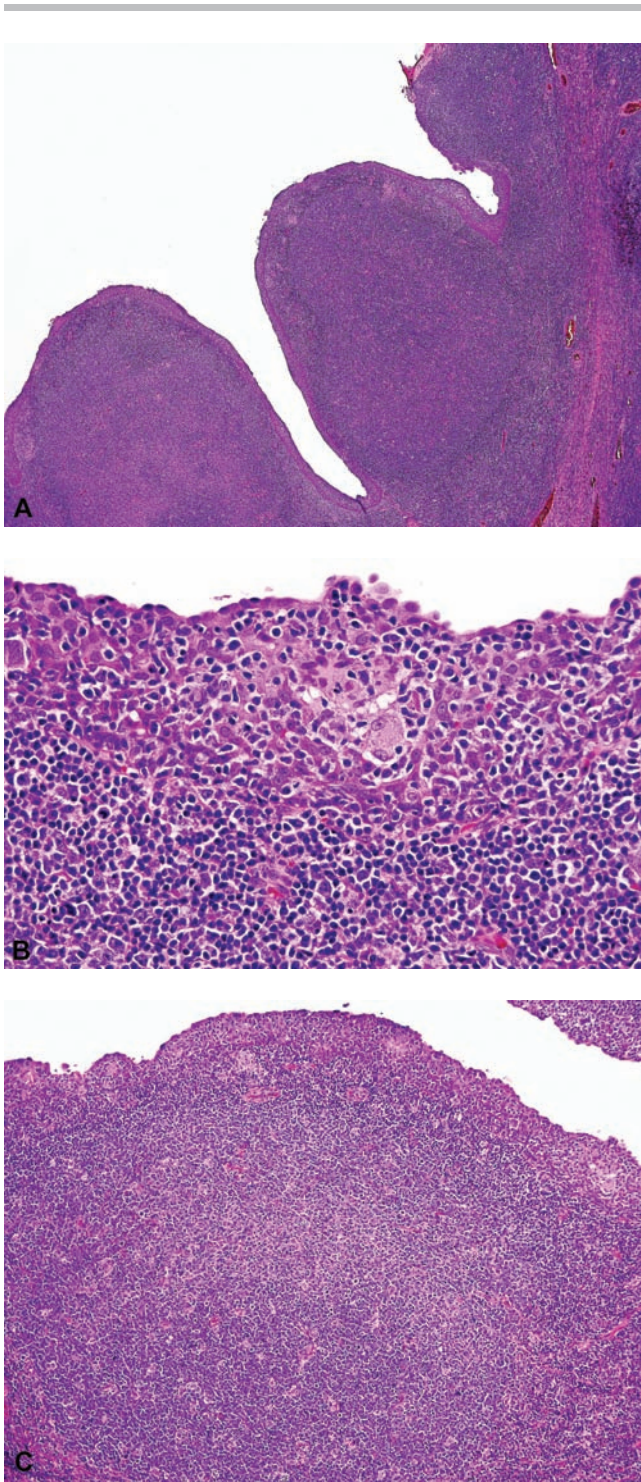


Figure 29 HIV-associated lymphoepithelial cyst of the parotid gland. (A) A cystic structure surrounded by dense lymphoid infiltrates with florid lymphoid follicular hyperplasia. (B) The cyst is lined by non-keratinized stratified squamous epithelium permeated by monocytoid lymphoid cells. (C) Irregularly shaped, large lymphoid follicle with germinal center. *Source:* Courtesy of Dr. Jean E. Lewis, Mayo Clinic, Rochester, Minnesota, U.S.A.

(Fig. 29B) (8). Monocytoid and/or marginal zone B cells do not expand into the interfollicular region, forming broad sheets. Lymphoepithelial lesions may

be present within the lymphoid infiltrate. The lymphoid follicles with germinal centers are large and sometimes confluent (Fig. 29C). The appearance of follicle lysis may be seen in the germinal centers, similar to that in lymph nodes of persistent generalized lymphadenopathy in HIV-positive patients.

The lymphoid follicles show a prominent network of CD21- and CD35-positive dendritic reticular cells. The HIV-1 major core protein (p24) and HIV-1 RNA are detected within the follicular reticular dendritic cells, indicating that there is active replication of the virus within them, but not in the salivary acinar cells or duct epithelial cells (5). Interfollicular regions consist of a mixture of small lymphocytes of both B- and T-cell types, plasma cells, and immunoblasts. T-cell population is dominated by CD8-positive cells rather than CD4-positive cells; this feature is contrary to HIV-negative LECs and LESA in Sjögren's syndrome (7). The lymphoid and plasma cell population is polyclonal in nature, revealed by immunohistochemical staining for immunoglobulin light chains and/or molecular analysis for immunoglobulin heavy chain rearrangement (7,8). Labial salivary gland biopsy of the patients with HIV-associated LEC most often discloses a focal lymphocytic sialadenitis with a focus score of more than 1, as in Sjögren's syndrome.

E. Tumor-Like Lesions

Sclerosing Polycystic Adenosis

This is a recently described, rare lesion of salivary glands of uncertain histogenesis that can simulate neoplasia clinically, radiographically, and histologically (1). The appearances resemble those of benign fibrocystic disease and sclerosing adenosis of the breast. There have been over 40 reported cases: four involved minor glands, including the buccal mucosa, hard palate, and floor of mouth (2,3), two the submandibular gland, and the remainder affected the parotid gland (1–8). The typical history is the presence of a slow-growing mass of less than two years duration with occasional pain and tenderness. The age range is from 9 to 80 years (3,6). Macroscopically, most lesions are well circumscribed but unencapsulated, with a minority forming multifocal nodules. They may contain multiple, small cysts. The maximum reported size is 7 cm in diameter. Microscopically, the lesions show a diverse range of appearances. They are characterized by densely collagenized, sparsely cellular fibrous tissue surrounding ill-defined salivary gland ductal and acinar lobules, and areas of cystically dilated ductal structures (Fig. 30). The latter are lined by epithelium, which can be attenuated or hyperplastic and may show intraluminal papillary projections. In addition, the lining may contain mucocytes, vacuolated cells, sebaceous-like cells, apocrine cells, and foci of squamous metaplasia (Fig. 30D). In some areas, interconnecting cellular bridges form a cribriform pattern (Fig. 30C), and this is occasionally associated with hyaline globules of basement membrane material forming collagenous spherules. Areas of atypical hyperplasia of densely granular,

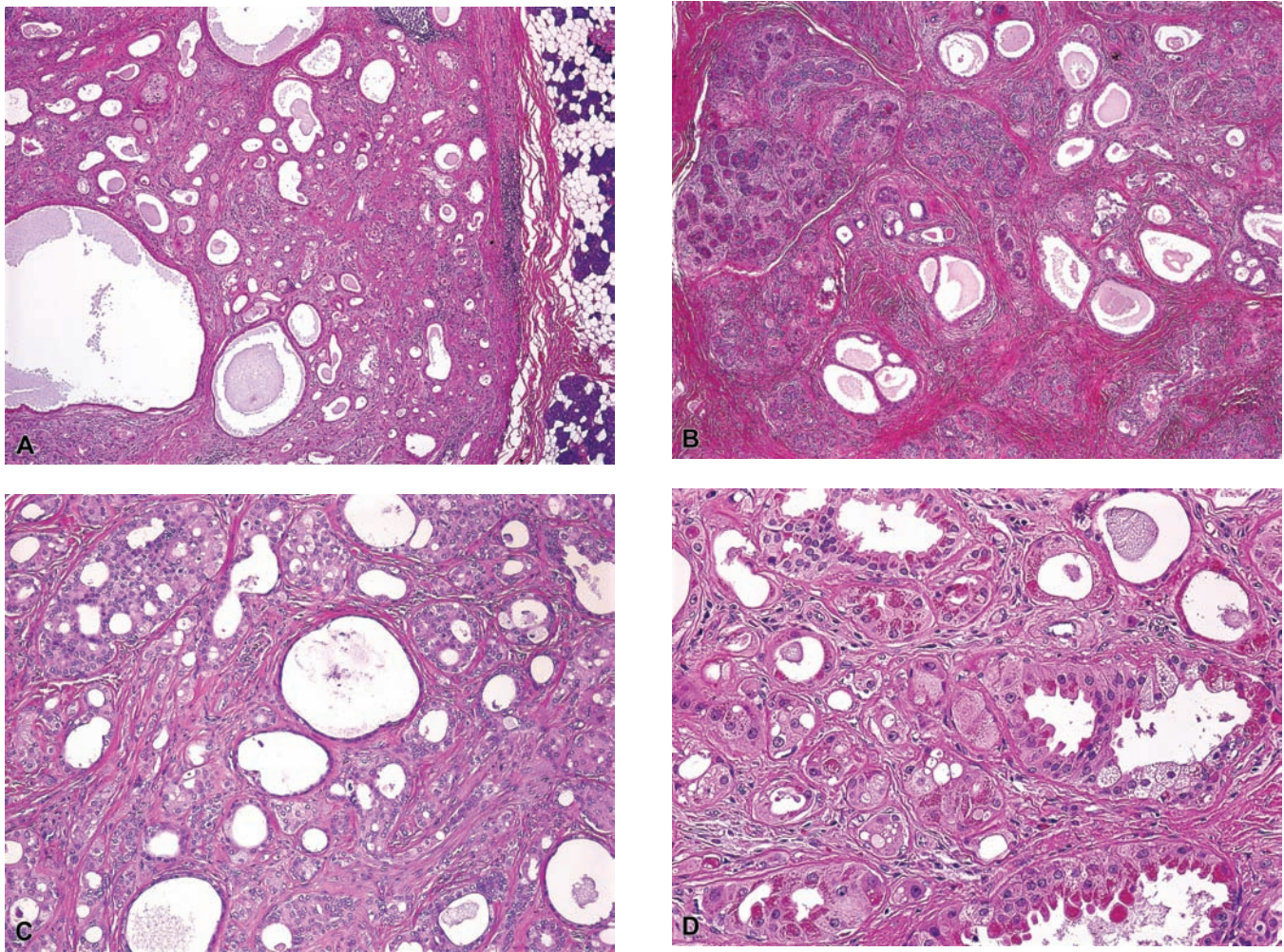


Figure 30 Sclerosing polycystic adenosis. (A) Well-circumscribed tumorous lesion composed of dilated ductal structures and fibrous stroma. (B) Densely collagenized fibrous tissue surrounding salivary gland ductal and acinar lobules. (C) Cystically dilated ductal structures and foci of cribriform areas accompanied by intervening collagenous stroma. (D) Ductal structures consisting of various cell types, including apocrine, acinar-like, vacuolated, and sebaceous-like cells. Note acinar-like cells exhibiting intracytoplasmic eosinophilic granules and conspicuous nucleoli.

eosinophilic, acinar cells can be readily mistaken for acinic cell carcinoma (Fig. 30D). In addition, there may be islands of more basophilic acinar cells in microcystic and solid configurations. In some cases, ducts show dysplastic changes resembling *in situ* carcinoma, and focal islands of similar cells have also been described (4). However, the lobular architecture is preserved, and staining with markers such as calponin (Fig. 31), smooth muscle actin, and muscle-specific actin shows a layer of myoepithelial cells surrounding the ducts and lobules (6). There is a variable mixed chronic inflammatory infiltrate, and in some areas xanthomatous macrophages are a conspicuous feature (Fig. 32). Two cases with a significant lipomatous component have been reported, and oncocytic change may also be seen (6). Immunoreactivity for estrogen and progesterone receptors has been demonstrated, suggesting the possible participation of hormone stimulation in the pathogenesis (4).

The most important differential diagnoses are acinic cell carcinoma, adenocarcinoma [not otherwise specified (NOS)] and cystadenocarcinoma. The lobular nature of polycystic sclerosing adenosis, together with the presence of a peripheral myoepithelial layer and the lack of evidence of infiltration, should prevent confusion.

The treatment of choice appears to be a complete but conservative local excision. About 30% of cases with adequate follow-up, however, have recurred with intervals ranging from approximately 5 to 22 years, and in a few cases, the recurrences were multiple. Although these recurrences are probably due to the presence of multifocal disease, the relatively high rate, together with the presence of dysplasia and/or carcinoma *in situ* means that the possible neoplastic potential of this process has yet to be fully characterised (4). A recent study using the polymorphism of the human androgen receptor (HUMARA) locus as a marker has shown sclerosing

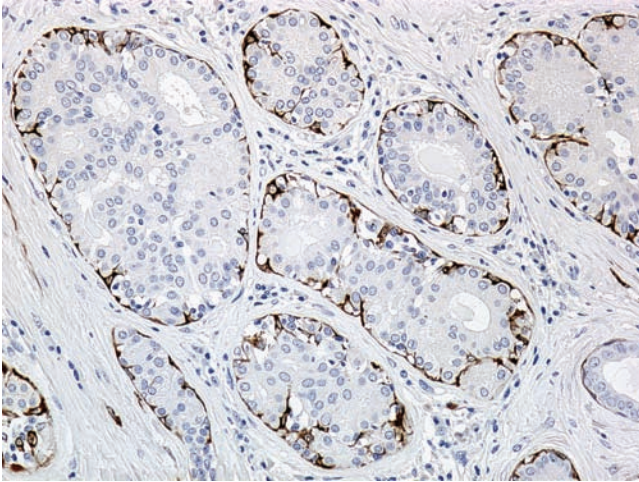


Figure 31 Sclerosing polycystic adenosis. Immunohistochemistry. Calponin-positive myoepithelial cells surrounding the hyperplastic ducts.

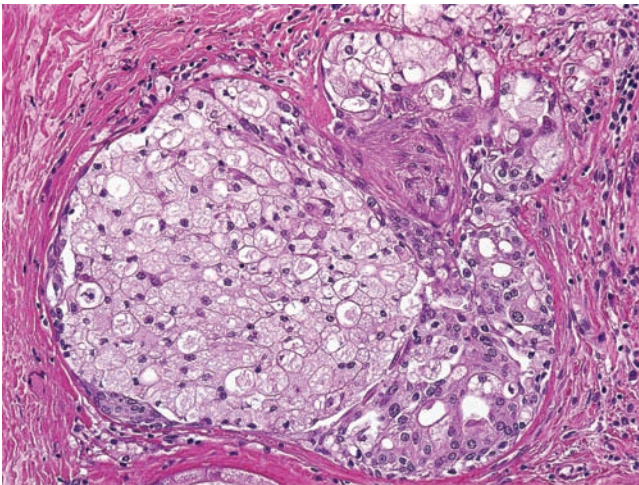


Figure 32 Sclerosing polycystic adenosis. Conspicuous aggregation of xanthomatous macrophages.

polycystic adenosis is clonal (9). This adds further support to the concept that it is a neoplastic rather than reactive process.

Sialosis

Sialosis (sialadenosis) is a noninflammatory and non-neoplastic, typically bilateral, salivary enlargement, usually involving the parotid glands (Fig. 33A) (1). Unilateral cases have been described (2), and in some patients, aplastic or hypoplastic parotid glands are present on the contralateral side (3,4). Sialosis has

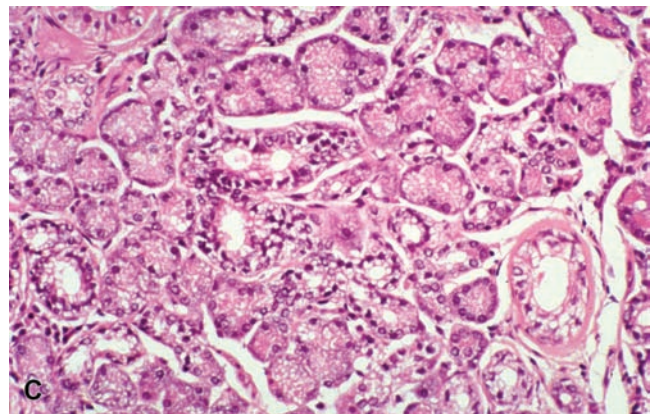
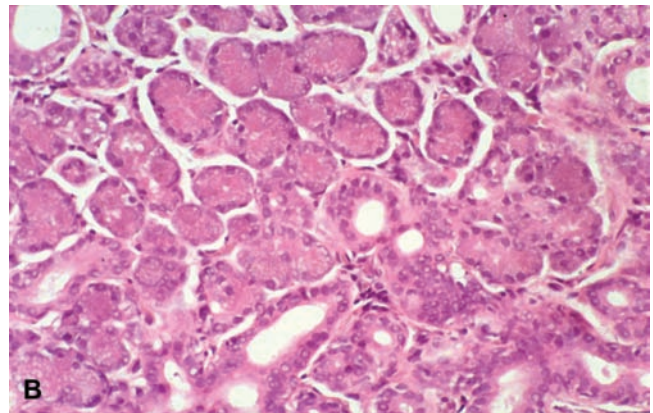


Figure 33 (A) Sialosis. Diabetic patient with bilateral parotid enlargement. (B) Sialosis. Enlarged granular serous cells and compressed striated ducts. (C) Sialosis. Enlarged serous cells have vacuolated cytoplasm.

been reported rarely in the submandibular gland (2) and intraoral minor glands in the palate (5). Although there are few major series, sialosis is probably more common than these would suggest, as many cases are regarded merely as facial adiposity.

The condition is usually painless, but occasionally the glands are tender or mildly painful. There is no sex predilection (6,7). The peak incidence is in the fifth and

Table 2 Causes of Sialosis

Drugs induced	Endocrine/metabolic	Nutritional
Antihypertensives	Acromegaly	Beriberi
Guanacine	Alcoholism	Bulimia
Iodine	Diabetes insipidus	Gastrointestinal disease
Isoprenaline	Diabetes mellitus	Malnutrition
Lead	Hypothyroidism	Pellagra
Mercury	Cirrhosis of the liver	Amylophagia
Naproxen	Uremia	Vitamin A deficiency
Oxphenbutazone		
Phenylbutazone		
Sulfisoxazole		
Thiocyanate		
Thiouracil		
Valproic acid		

sixth decades, and the main complaint is a slowly enlarging and cosmetically unsightly swelling of the parotids. Occasionally, patients may experience a dry mouth or sialorrhea. Although raised salivary levels of potassium and amylase have been reported, this is of limited, if any, practical value in diagnosis (4). Sialosis has been associated with a wide variety of factors that are predominantly nutritional, metabolic or pharmaceutical (4,8) (Table 2). It is thought that a unifying etiopathogenesis could be related to peripheral autonomic nerve dysfunction (9). A relationship with salivary aquaporin water channels has been recently suggested (10).

The most common causes are diabetes mellitus and alcohol misuse. The reported prevalence of sialosis in diabetes ranges from 10% to 80% (11), and in recent study, nearly half the patients with sialosis were diabetic (4). Sialosis can occasionally precede clinically detectable hyperglycemia. Alcohol misuse, particularly when associated with cirrhosis, has been reported to lead to sialosis in 30% to 60 % of these patients (7,12–14), but this high frequency has been questioned (4). Any long-standing nutritional disorder can result in sialosis, and this may also be a factor in some alcoholic patients. A number of cases related to patients with bulimia or anorexia nervosa have been reported (15,16), and these may also be associated with palatal necrotising sialometaplasia (17). However, in a significant number of patients with sialosis, no cause is found (18).

Sialosis is rarely biopsied. Microscopy shows acinar cell hypertrophy, and the cells can be two or three times the normal size (19). The enlarged cells can have granular cytoplasm packed with densely staining zymogen granules (Fig. 33B), or the cytoplasm can be vacuolated (Fig. 33C). Some cases show a mixed population. Compression of the striated ducts has been described (20), but inflammation is not a feature. In long-standing cases, parenchymal atrophy and fatty replacement can be seen (21). Nutritional and drug-related sialosis will often regress if the underlying causative factors are eliminated, but in cases due

to diabetes and chronic alcohol misuse, sialosis usually persists despite treatment (22). Superficial parotidectomy is sometimes undertaken to correct unacceptable cosmetic deformity (2).

Salivary Gland Hyperplasia

The terminal duct of salivary glands is a unit consisting of the secretory acinus, intercalated duct, and associated myoepithelial cells. Hyperplasia of this complex can result in two distinct forms: acinar adenomatoid hyperplasia and ductal adenomatoid hyperplasia (1,2).

Acinar adenomatoid hyperplasia is a rare, idiopathic condition, which usually affects the intraoral minor salivary glands, with the palate accounting for the majority of cases (3). It typically presents as a painless, sessile swelling at the junction of the hard and soft palates and clinically it can mimic a salivary gland tumor. The sex ratio is equal, and the majority of patients are middle aged or elderly. Most cases have been reported in Caucasians, and the condition appears to be very uncommon in Asians (4). There is no association with sialosis (sialadenosis) of the major salivary glands.

Microscopy shows lobules of hyperplastic but otherwise unremarkable mucous acinar cells and essentially normal-appearing ducts (Fig. 34). In most cases, the overlying palatal epithelium is normal, but one case showed a lichenoid reaction, and in another, pseudoepitheliomatous hyperplasia was reported. Occasionally, there are areas of interstitial mucous extravasation with an associated inflammatory reaction. The condition is entirely benign, and excision is curative. A similar condition causing swelling in the sublingual region has been called "idiopathic hyperplasia of the sublingual gland" (5,6) or "pouting" sublingual glands. This is seen as an enlargement in the floor of the mouth in totally or partially edentulous patients. The sublingual glands may be otherwise normal or show nonspecific chronic inflammation.

Ductal adenomatoid hyperplasia (also known as intercalated duct hyperplasia) is also very rare and is usually seen as a chance finding in surgical specimens from major salivary glands, especially tumor resections. There is a 3:1 male predominance, and most cases are seen in the sixth decade.

Microscopy shows one or several unencapsulated foci of proliferation of ducts with structural similarities to the normal intercalated ducts (Fig. 35). These are densely packed with little supporting stroma and consist of an inner layer of cuboidal cells and an outer layer of myoepithelial cells. There may be residual areas showing acinar differentiation with cells containing basophilic zymogen granules.

The salivary gland tumor most frequently associated with ductal adenomatoid hyperplasia is epithelial-myoeplithelial carcinoma. This has raised speculation that it may be a precursor of this tumor. This could also explain the frequent presence of an element of epithelial-myoeplithelial carcinomas in hybrid salivary tumors (2,7).

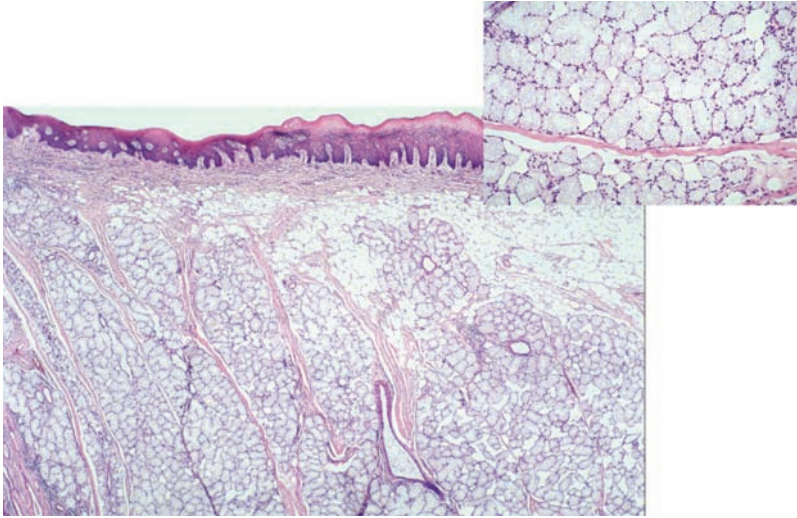


Figure 34 Adenomatoïd hyperplasia of palate showing hyperplastic but otherwise normal mucous acini.

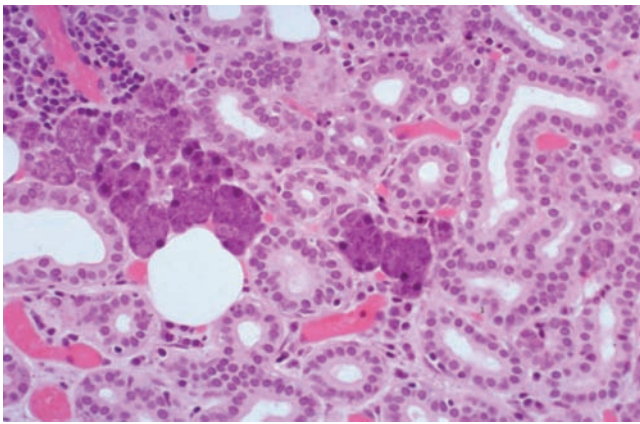


Figure 35 Ductal adenomatous hyperplasia showing duct-like structures and residual serous acini.

F. Lymphoepithelial Sialadenitis and Sjögren's Syndrome

Introduction

Lymphoepithelial sialadenitis (LESA) is histologically characterized by conspicuous interstitial lymphocytic infiltration accompanied by atrophy of the salivary gland parenchyma and formation of lymphoepithelial lesions (epimyoepithelial islands). This pathologic condition often, but not always, occurs in the patients who fulfil the clinical criteria of Sjögren's syndrome, but up to 50% of LESA also develops in the patients without the clinical features of Sjögren's syndrome; they may or may not be associated with other connective tissue disease, especially rheumatoid arthritis (1).

Conversely, almost all patients with Sjögren's syndrome manifest LESA.

Historically, the pathologic entity now called LESA was first described by Mikulicz in 1892 (2). He reported a 42-year-old man with bilateral, painless enlargement of the salivary and lacrimal glands associated with an infiltration of small round cells. Later, the cases with bilateral salivary or lacrimal enlargement were diagnostically divided into two groups: "Mikulicz's disease" and "Mikulicz's syndrome" (3). The term Mikulicz's disease has been used when the cause of the lesion is not defined, while the term Mikulicz's syndrome encompasses cases with many known different underlying entities, including tuberculosis, sarcoidosis, and lymphoma. However, the separation of these two categories is ambiguous and does not provide any meaningful prognostic or therapeutic information; to prevent confusion, they should no longer be used. In 1933, Sjögren described detailed clinical and histologic findings in women presenting with xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes) (4). In 1953, on the basis of the observation of cases diagnosed as Mikulicz's disease, Morgan and Castleman reported that there are many similarities between their cases and those described in Sjögren's syndrome and concluded that Mikulicz's disease is only one manifestation of the generalized symptom complex of Sjögren's syndrome (5). On the other hand, recently Mikulicz's disease has been reported to be associated with elevated IgG4 concentrations in the serum (6).

The term LESA was formerly referred to as benign lymphoepithelial lesion or "myoepithelial sialadenitis" (7), but these two names are not appropriate from the clinicopathologic point of view (1). It has become evident that some of the cases described as benign lymphoepithelial lesion, a term first introduced by Godwin in 1952 (8), on the basis of the recent advances of immunohistochemical, flow

cytometric, and molecular genetic studies, were actually lymphomas (1,9,10). Furthermore, the term myoepithelial sialadenitis, alternatively applied for the lesion later, is also misleading from the morphogenetic aspects; the constituting nonlymphoid cells are mainly basal type of epithelial cells rather than myoepithelial cells (11,12). LESA, introduced by Harris in 1999, seems to be an accurate term that refers to the specific histopathologic features, and it has now become generally accepted (1).

Clinical features

Patients with LESA and Sjögren's syndrome are typically women, with the female-to-male ratio being 9:1. The disease can present at any age, with a significant peak incidence from fourth to sixth decades. The lesion presents as unilateral or bilateral diffuse, painless or mildly painful, firm enlargement of the salivary glands and/or lacrimal glands. LESA most frequently involves the parotid gland (80–85%), followed by the submandibular gland (10–15%) usually in combination with the parotid enlargement (7). Swellings of the minor glands are rare, but subclinical focal periductal lymphocytic infiltrates are almost always seen in the labial salivary glands in patients with Sjögren's syndrome.

Population prevalence of Sjögren's syndrome is about 0.5%; it is one of the most common autoimmune disorders together with rheumatoid arthritis and systemic lupus erythematosus (13). Sjögren's syndrome is clinically characterized by the presence of keratoconjunctivitis sicca or xerophthalmia (dry eyes) and xerostomia (dry mouth), caused by the involvement of the lacrimal and salivary glands. Sjögren's syndrome is classified into two forms: primary (or sicca complex) and secondary. Both types have dry mouth and eyes, but in secondary Sjögren's syndrome, there is the presence of one or more additional autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, primary biliary cirrhosis, and others. The involvement of the lacrimal and salivary glands by lymphocytic infiltration impairs the production of tears and saliva, leading to dry eyes and dry mouth. Dry mouth is accompanied by difficulty in swallowing and speaking, alterations in taste, dental caries, and candidiasis. One-third of the patients also present with systemic extraglandular manifestations involving predominantly skin, lung, heart, kidneys, nervous and hematolymphoid systems.

Autoantibodies specific for Ro (SS-A) and La (SS-B) are strongly associated with Sjögren's syndrome and are of major importance in diagnosis. Clinically, the Ro/La immunoglobulin A (IgA) titers are proven to be positively correlated with sicca symptoms and anti-Ro levels with the occurrence of diverse systemic disease manifestations. Rheumatoid factors are also positive in approximately 60% of the patients. Several viruses and genetic predispositions have been implicated in the development of Sjögren's syndrome. Histologically similar changes to LESA can occur in HIV- and hepatitis C virus (HCV)-infected patients (14,15). However, despite extensive research

on the underlying cause of Sjögren's syndrome, the exact etiology and pathogenesis remain unresolved. Comprehensive reviews of recent progress on the clinical aspects and the putative pathogenetic mechanism operating in the development of Sjögren's syndrome are available elsewhere (16,17).

Until recently, several schemes of diagnostic criteria for primary Sjögren's syndrome have been proposed. In 2002, an American-European consensus group suggested a set of diagnostic criteria (Table 3) (18). Diagnosis of primary Sjögren's syndrome requires four of six criteria, including subjective or objective signs and symptoms of dryness, a characteristic appearance of a biopsy sample from a minor salivary gland, and the presence of an autoantibody such as anti-SS-A/SS-B. Exclusions from the assessment of the criteria include previous radiotherapy to the head and neck, lymphoma, infection with HCV, human T-lymphotropic virus type I, or HIV, sarcoidosis, and graft-versus-host disease. Also, measurements of tear and saliva flow must be made in the absence of drugs that have anticholinergic side effects.

The majority of LESA cases are of a chronic and indolent nature. However, patients with LESA, whether or not associated with Sjögren's syndrome, have a 44-fold increased risk of developing lymphoma, of which 80% are extranodal marginal zone B-cell lymphoma (MALT lymphoma) (1). The rate of development of lymphoma is estimated to be approximately 4% to 7% of the patients with LESA (1). The presence of progressive unilateral swelling of an enlarged parotid gland, lymphadenopathy, splenomegaly, anemia, lymphopenia, peripheral neuropathy, cutaneous vasculitis, and type II mixed monoclonal cryoglobulinemia is suggestive of lymphoma (16). Therefore, careful observation with close follow-up is required for patients with LESA and Sjögren's syndrome. Therapy for symptomatic control includes topical agents to improve moisture and decrease inflammation for dry mouths. Systemic steroids may be used, but at present there are no established medication strategies for the treatment of patients with severe systemic manifestations.

Pathology

Grossly, LESA presents as a diffuse enlargement of the salivary glands or a nodular formation, which is yellow to tan and resembles lymph node tissue. The latter appearance is sometimes mistaken for a true neoplasm. The overall lobular architecture and the capsule of the major salivary glands are maintained.

The histologic hallmarks of LESA are dense lymphocytic infiltration, acinar atrophy, and areas of lymphoepithelial lesion, previously referred to by the inaccurate term epimyoeplithelial islands, which show various developmental stages (Figs. 36, 37). Initially, small lymphocytic infiltrates are limited to around the intralobular salivary ducts (Fig. 36). Subsequently, lymphocytic infiltration gradually increases and replaces the parenchyma, resulting in marked acinar atrophy or loss (Fig. 37A). The lobular architecture of the normal glands and interlobular septa are generally preserved. Lymphoid follicles with germinal center

Table 3 International Classification Criteria for Sjögren's Syndrome Proposed by the American-European Consensus Group

I. Ocular symptoms:
— A positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms:
— A positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs:
— That is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer's I test, performed without anaesthesia (≤ 5 mm in 5 min)
2. Rose Bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system)
IV. Histopathology:
— In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1 , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm ² of glandular tissue
V. Salivary gland involvement:
— Objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (≤ 1.5 mL in 15 min)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory, or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI. Autoantibodies:
— Presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both
Rules for classification
- For primary Sjögren's syndrome:
— In patients without any potentially associated disease, primary Sjögren's syndrome may be defined as follows:
a. The presence of any 4 of the 6 items is indicative of primary Sjögren's syndrome, as long as either item IV (Histopathology) or VI (Serology) is positive.
b. The presence of any 3 of the 4 objective criteria items (i.e., items III, IV, V, VI).
c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiologic survey.
- For secondary Sjögren's syndrome:
— In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary Sjögren's syndrome.
Exclusion criteria:
- Past head and neck radiation treatment
- Hepatitis C infection
- AIDS
- Preexisting lymphoma
- Sarcoidosis
- Graft-versus-host disease
- Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

Abbreviation: AIDS, acquired immunodeficiency syndrome.

Source: From Ref. 18.

formation may be present in areas of dense lymphoid infiltration. The interfollicular lymphoid infiltrate constitutes a mixed population of polyclonal small B- and T-cell lymphocytes, scattered immunoblasts, histiocytes, and sometimes considerable numbers of plasma cells.

Residual ductal epithelium, on the other hand, proliferates together with the permeation of lymphocytes into the epithelium (Fig. 37B). Eventually, there is luminal obliteration, and the characteristic lymphoepithelial lesions develop. The permeating lymphocytes are monocytoïd and/or marginal zone B cells. They are intermediate in size with irregularly shaped nuclei and abundant pale cytoplasm, somewhat resembling centrocytes. The monocytoïd and/or

marginal zone B cells are confined within the lymphoepithelial lesions. Monoclonality of lymphocytes by means of gene rearrangement analysis using polymerase chain reaction can be demonstrated in LESA without any histologic evidence indicative of lymphoma (1,15,19,20). The irregularly shaped epithelial component of the lymphoepithelial lesions consists of polygonal or plump spindle cells exhibiting uniform elongated nuclei with fine chromatin and indistinct nucleoli. The epithelial cells exhibit no atypia, and mitoses are rare. The lymphoepithelial lesions may undergo squamous metaplasia, in rare cases being accompanied with keratinization. Foci of hyaline basement membrane-like material may be occasionally observed among the cells of the lesions. These lymphoepithelial lesions

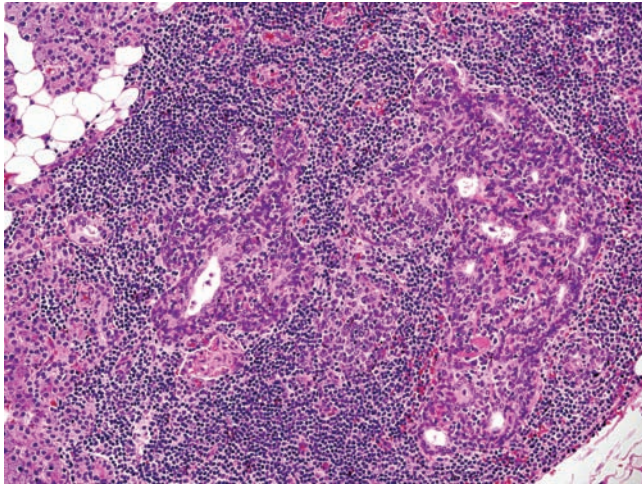


Figure 36 Lymphoepithelial sialadenitis of the parotid gland. Marked small lymphocytic cell infiltration is evident around the salivary ducts accompanied by the formation of lymphoepithelial lesions (epimyoeptithelial islands).

were previously considered to be composed of both ductal epithelial cells and myoepithelial cells; thus the term epimyoeptithelial islands has been used for a long time. However, recent immunohistochemical studies suggest a lack of myoepithelial cell participation, as mentioned above (11,12). Cystically dilated salivary ducts may uncommonly be observed.

The histologic feature of LESA seen in the major salivary glands can occur in the minor salivary glands of the patient with Sjögren's syndrome. In the minor salivary glands, however, the typical histologic picture is described as focal lymphocytic sialadenitis, and lymphoepithelial lesion, an essential finding of LESA in the major salivary glands, is rarely encountered (Fig. 38). The histologic appearance of a labial biopsy sample is one of the important features for diagnosis of Sjögren's syndrome (21). In the patients with Sjögren's syndrome, even without apparent clinical enlargement, characteristically there are greater than or equal to one focus score, where a focus is defined as a focal lymphocytic aggregate consisting of more than 50 lymphocytes per 4 mm² of salivary gland tissue adjacent to normal-appearing mucous acini (18). At least four lobules in the biopsy sample are required for the assessment.

Differential Diagnosis

Differential diagnoses of LESA include malignant lymphoma, lymphoepithelial carcinoma, lymphadenoma, chronic nonspecific sialadenitis, and HIV-associated lymphoepithelial cysts (LECs).

The distinction between LESA and malignant lymphoma, especially of extranodal marginal zone B-cell type (MALT lymphoma), may be difficult and is still a controversial issue (see also the section "Malignant Lymphomas") (1,5,19,20,22). Monocytoid

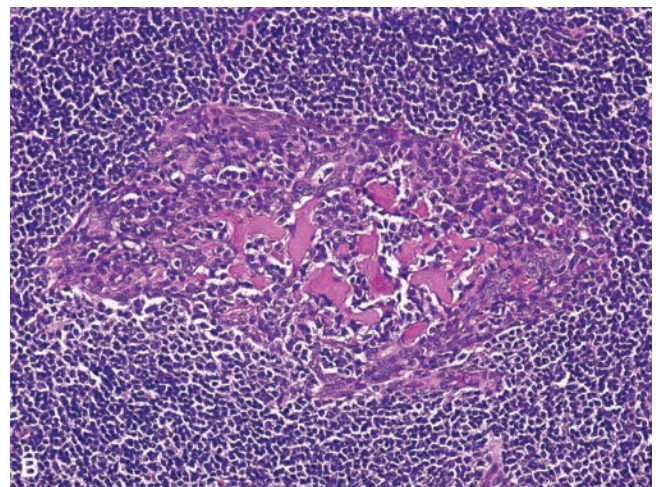
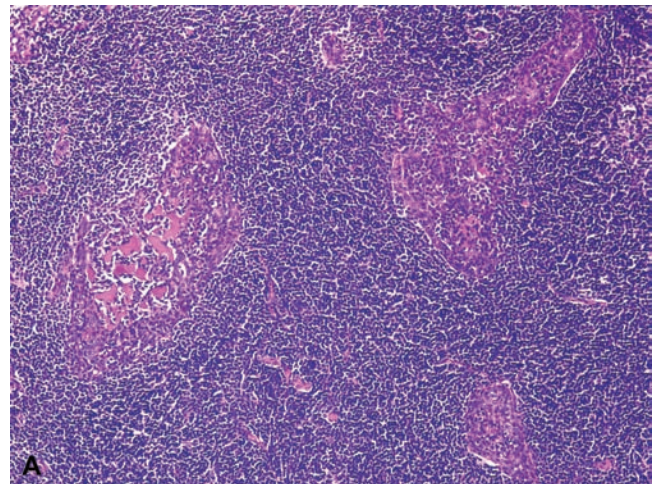


Figure 37 Lymphoepithelial sialadenitis of the parotid gland. (A) Several well-developed lymphoepithelial lesions (epimyoeptithelial islands) are present within a dense lymphoid infiltration. (B) The lymphoepithelial lesion is characterized by the proliferation of ductal epithelium and the permeation of monocytoïd type lymphocytes. Foci of hyaline basement membrane-like material are also observed among the cells of the lesions. Note that the formation of a halo of monocytoïd cells around the lymphoepithelial lesions is not evident. Monoclonality of the lymphoid cells was not proven by means of immunohistochemical and molecular genetic studies in this case.

and/or marginal zone B cells may be prominent inside the lymphoepithelial lesions in LESA, but if these cells are present outside the lymphoepithelial lesions and form either broad halos or confluent areas in interfollicular regions, MALT lymphoma should be considered (1). In addition, the presence of sheetlike proliferation of plasma cells, with or without Dutcher bodies, also favors a diagnosis of lymphoma. Furthermore, the demonstration of monoclonality by immunohistochemistry or flow cytometry gives supportive evidence of MALT lymphoma rather than LESA.

Both lymphoepithelial carcinoma, formerly sometimes referred to as "malignant lymphoepithelial

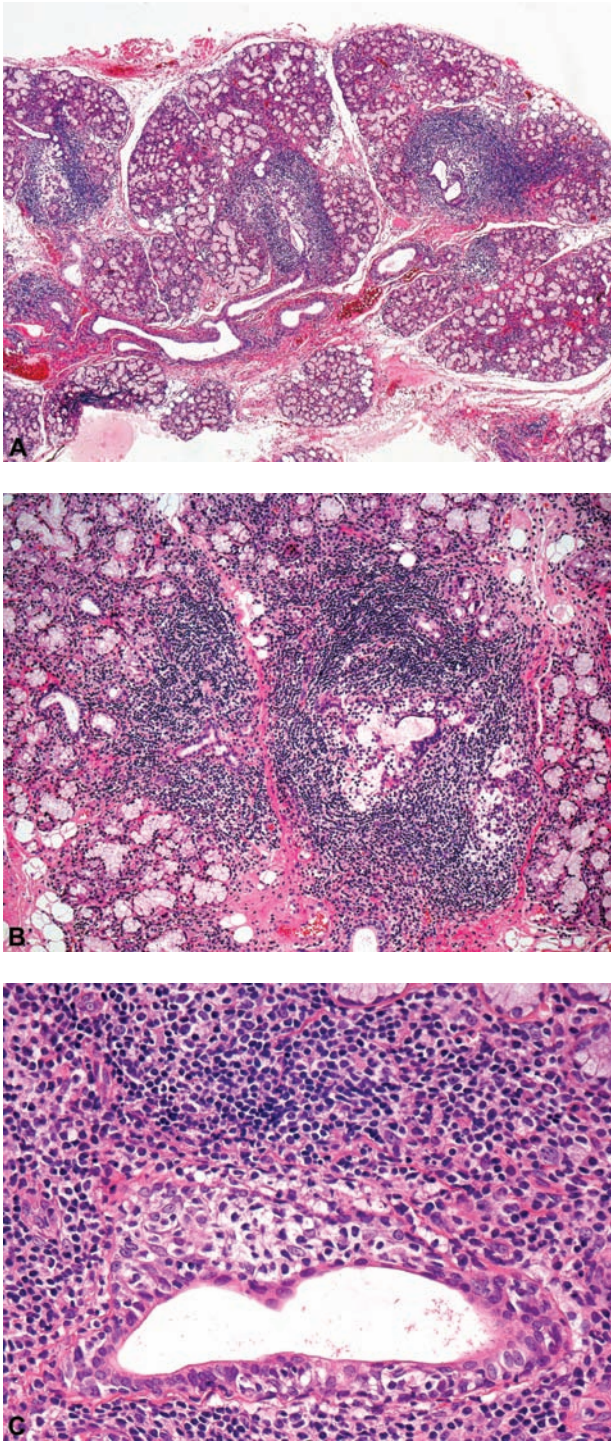


Figure 38 Sjögren's syndrome. Labial biopsy specimen. (A) Low-power view shows several foci of periductal lymphoid aggregates in the labial minor salivary gland. (B) Foci of small lymphocytic aggregation around the intralobular ducts accompanied by lymphoepithelial lesions (epimyoeplithelial islands) are evident. In general, lymphoepithelial lesions characteristic of lymphoepithelial sialadenitis in the major salivary glands are uncommonly observed in the minor salivary glands. (C) High-power view demonstrates small lymphocytes and plasma cells infiltrating periductal area and the formation of the early stage of lymphoepithelial lesion consisting of the duct epithelium permeated by monocytoid lymphoid cells.

lesion," and LESA are composed largely of two elements: epithelial nests and lymphoid infiltrate. Lymphoepithelial carcinoma may rarely arise in the setting of a LESA-like lesion. Unlike lymphoepithelial carcinoma, however, epithelial cells constituting lymphoepithelial lesion in LESA lack nuclear atypia, coarse chromatin pattern, and mitotic activity. Lymphoepithelial carcinoma often infiltrates into the surrounding salivary gland tissues accompanied by lymphoid stroma. Additionally, epithelial nests of lymphoepithelial carcinoma are larger and have a more irregular outline than those of LESA. Moreover, the presence of EBV revealed by EBV-encoded small RNA (EBER) in situ hybridization, over-expression of p53, and high-cell proliferative activity may be useful for distinguishing lymphoepithelial carcinoma from LESA (23). Lymphadenoma is a rare benign neoplasm composed of variable-sized islands of epithelial cells enclosed within a prominent lymphocytic infiltrate similar to LESA, but in contrast to LESA, lymphadenoma is a well-circumscribed lesion (24).

Chronic nonspecific sialadenitis is sometimes confused with LESA, but in the former, the inflammatory infiltrate usually consists of a mixture of lymphocytes, plasma cells, and macrophages, as well as neutrophils, and is associated with prominent fibrosis. In addition, there are no well-developed lymphoepithelial lesions (14,21,25). Lymphoid hyperplasia can develop in the salivary glands, especially the parotid gland, in the patients with HIV infection. In such instances, referred to as HIV-associated LECs, dilatation of the residual ducts is more pronounced than in LESA (26).

G. Introduction to Salivary Gland Tumors

Epidemiology

There have been few large-scale studies on the epidemiology of salivary gland neoplasms (1). In addition, there has been considerable variation in how data have been interpreted. For example, some studies have included only parotid tumors, or tumors in the major salivary glands. In some cancer registries only malignant salivary tumors are recorded. In one study, Warthin's tumor, which is the second most common salivary neoplasm, was excluded from the series (2). Several investigators have highlighted the possibility that their quoted incidence rates, for benign tumors particularly, were underestimates (1,3,4). When all salivary gland tumors are included, the global annual incidence rates have ranged from 0.4 to 13.5 cases per 100,000 patients (5). The annual incidence for malignant salivary gland tumors only, varied from 0.4 to 2.6 cases per 100,000 population (1,6–8). Malignant salivary gland tumors accounted for 6% of head and neck cancers and 0.3% of all malignant neoplasms in the United States between 1973 and 1988 (9). There have been a limited number of studies reporting time trends in the incidence, but several have suggested an increasing frequency since the 1980s, particularly in

the elderly population (10–13). In the United States, there appears to have been a significant increase in the incidence of malignant salivary gland tumors during the period 1974 to 1999 (1.0–1.1/100,000 population). In addition, salivary neoplasms accounted for 8.1% of all head and neck tumors during this period (14). In the older literature there is an equal sex incidence in white Americans and a slightly increased incidence in the black population (15). However, a more recent study showed a slight male predominance (M:F 1.5:1) (6). Although the data on geographic distribution and ethnicity are limited, in most reports there appears to be minimal variation in incidence or the distribution of individual tumor types. One exception to this was the very high incidence of lymphoepithelial carcinomas in the North American Inuit population in the middle of the twentieth century (16,17). At that time these tumors accounted for 25% of all malignancies in this population. Since then there has been a significant decline in its frequency. In Malaysia there is a higher frequency of salivary tumors in ethnic Malays than Indians or Chinese (18). A higher relative frequency of malignant intraoral salivary gland tumors has been reported in a Chinese population (19).

Site, Age, and Sex Distribution

In major series, the parotid gland is the site of between 64% and 80% of all salivary primary epithelial tumors (20). Seven percent to eleven percent of tumors involve the submandibular glands, and less than 1% occur in the sublingual glands. Tumors in the minor glands account for 9% to 23% of cases (5,21–24). Fifty-four percent to seventy-nine percent of these are benign and 21% to 46% are malignant. There are striking variations in the ratio of benign to malignant tumors in different sites. For example, malignant tumors comprise 15% to 32% of parotid tumor, 41% to 45% of submandibular tumors, and the large majority of sublingual tumors (~90%). About half of minor gland tumors are malignant (19,25), and there appears to be variations in the frequency, age distribution, and sex ratio in different populations (26). In the floor of the mouth, tongue, and retromolar trigone between 80% and 90% of salivary tumors are malignant (5). Although there is a slight overall female predominance, the sex ratio varies in different tumor types. There is a wide age distribution with a peak incidence in the fifth decade. Pleomorphic adenoma is the most common tumor and accounts for over half of salivary tumors in most large series. The second most common neoplasm is Warthin's tumor, which typically forms about 10% to 15% of cases.

Etiology

Viruses. Several viruses have been implicated in the development of salivary tumors. However, the only strong association is between EBV and lymphoepithelial carcinoma (27–29). Although the large majority of cases of this tumor affect Asians (30) and Greenlandic Inuits (31), sporadic cases are reported

in nonendemic regions (32). Most studies have not detected EBV in other salivary gland tumors or normal parotid gland (28,33). However, EBV has been reported in several cases of intranasal pleomorphic adenoma (34). No etiologic role has been found for cytomegalovirus in benign parotid tumors (33). Pleomorphic adenomas have been shown to contain Simian virus 40 (SV40) DNA sequences and express the SV40 large T antigen (35), but no association has been found with polyoma virus or papillomavirus in human salivary tumors.

Radiation. There is strong evidence for a close association between ionizing radiation and salivary gland tumors. In survivors of the atom bomb explosions in Hiroshima and Nagasaki, there was a 3.5× relative risk of developing benign salivary tumors and an 11× increased risk for malignant tumors (36–39). In addition, the relative risk was directly related to the distance from the epicenter of the explosions and the level of exposure to ionizing radiation. There was a high frequency of both Warthin's tumor and mucoepidermoid carcinoma in these patients (40). Therapeutic radiation of the head and neck has also been implicated in salivary gland neoplasia. This is typically a late consequence and can result in both benign and malignant tumors (41–44). Iodine¹³¹ used to treat thyroid disease is also concentrated in salivary glands and increases the risk of salivary tumors (45). Routine dental diagnostic radiographs may also be associated with an increased risk (46,47). There is also evidence of an association between cutaneous and salivary neoplasms, with both showing a pattern of incidence suggestive of susceptibility to ultraviolet radiation exposure (48,49). There is an increased risk of predominantly malignant salivary tumors in survivors of childhood cancer in the head and neck region that had been treated by a combination of chemotherapy and radiotherapy (50). The relationship, in any, between salivary tumors and high-frequency electromagnetic fields from cellular telephones is contentious, but most large-scale studies show no increased risk (51,52). However, a recent study of a population with higher than average mobile telephone use appears to show a higher frequency of benign parotid tumors (53). There is no excess incidence of salivary tumors in those exposed to radon gas (54).

Occupation. There is increased risk of developing salivary gland tumors in a diverse range of industries, including rubber manufacturing (55,56), plumbing (57), and woodworking in the automobile industry (58). Exposure to nickel compounds (56), formaldehyde, and solvents has been implicated (59). There appears to be a higher incidence of salivary gland cancer in women working in hairdressing and beauty shops (60,61). However, there is no increased risk from the personal use of hair dyes (62). In Quebec there was an increased risk in populations living close to asbestos mines, and the risk was directly related to the distance from the mines (63).

Lifestyle and nutrition. The majority of studies have failed to demonstrate an association between most salivary gland tumors and either cigarette

smoking or alcohol consumption (64–66). One study showed an elevated risk in men but not women (56). However, there is a close association between cigarette smoking and Warthin's tumor, and this is discussed in section "Warthin's tumor," page 525. There has only been one study on the relationship, if any, between diet and the development of salivary tumors (67). This appeared to show an inverse relationship between salivary gland tumors and consumption of antioxidant vitamins, beans, and carotenoids. It was suggested that high blood cholesterol was associated with an increased risk. Exposure to silica dust and kerosene as a cooking fuel appeared to increase the risk of salivary gland cancers in a Chinese population (68). In a European study, a higher level of malignant salivary gland tumors has been associated with exposure to nickel, chromium, asbestos, and cement dust (69). There is a single retrospective controlled study suggesting an increased prevalence of type II diabetes and obesity in patients with salivary gland tumors (70).

Hormones. Although sex steroid hormone receptors have been described in normal and neoplastic salivary glands, there have been conflicting reports. Estrogen receptors were found in normal salivary glands in both men and women (71). It was also reported that half of the salivary tumors in women had estrogen receptor levels comparable with those seen in hormonally dependent breast tumors. However, other workers have failed to confirm these findings and the methodology has been questioned (72). Estrogen receptors have been reported in a minority of mucoepidermoid carcinomas, acinic cell carcinomas (73), and salivary duct carcinomas (73). No estrogen receptors have been reported in adenoid cystic carcinomas (72–76). Estrogen receptors have been reported in some pleomorphic adenomas (73,77,78), but others have failed to confirm this finding (79). Reduced expression of estrogen receptor- β in salivary duct carcinoma was associated with adverse clinical features (80). Progesterone receptors have been reported in normal salivary glands (74,81) and in a minority of pleomorphic adenomas (73,81). Interestingly, high levels of progesterone receptors have been reported in recurrent pleomorphic adenomas (81). However, another study failed to show evidence of these receptors in any of the benign salivary gland tumors examined (79). Progesterone receptors were found in 2 of 10 acinic cell carcinomas and 3 of 10 mucoepidermoid carcinomas, but were not detected in salivary duct carcinomas (82). Adenoid cystic carcinomas have been positive for progesterone receptors in some studies (74,83), but either infrequent or negative in others (72,73). Androgen receptors are seen in the large majority (~90%) of salivary duct carcinomas (84–86). In addition, androgen receptors were detected in all the cases of salivary duct carcinoma, carcinoma ex pleomorphic adenoma, and basal cell carcinomas examined in one study (79). A fifth of the acinic cell carcinomas, mucoepidermoid carcinomas, and adenoid cystic carcinomas were positive for androgen receptors but all the benign tumors were negative.

Imaging

When dealing with salivary gland diseases, a detailed clinical history and physical examination will usually lead to a reasonable clinical diagnosis. Salivary gland diseases such as self-limiting entities like viral parotitis may not require any imaging studies. However, imaging is often necessary to confirm the clinical findings and determine the location and extent of pathologic changes.

Ultrasound, CT, and MRI are the most common imaging procedures for the diagnosis of mass-forming lesions of the salivary glands (1–8). In Europe and Japan, ultrasound is frequently the first imaging modality used to assess superficial salivary gland lesions, with accuracy similar to that of CT and MRI (3,4,7). Neoplasms are always hypoechoic relative to the normal hyperechoic glandular tissue. Although ultrasound can also be used to guide fine-needle aspiration cytology or core needle biopsy to confirm their benign or malignant nature, it cannot evaluate the deep lobe of the parotid gland and the extent of large tumors. In such circumstances, CT and MRI play an important role instead. MRI is particularly useful in assessing perineural, vascular, meningeal, and skull base invasion (5). Additionally, CT and MRI are helpful in the evaluation of cervical lymph nodes for metastasis. Minor salivary gland neoplasms are often difficult to assess on clinical examination, and the use of preoperative CT or MRI is important for the determination of the tumor extent. In many cases, however, accurate discrimination between benign and malignant tumors and the prediction of the histology of tumors are not possible on ultrasound and/or CT as well as MRI studies.

Almost all parotid gland tumors are readily identified on T1-weighted MRI as a lesion with low signal intensity relative to the high signal intensity of the background. Pleomorphic adenomas generally have high signal intensity on T2-weighted images, whereas a mass of intermediate or low signal intensity on T2-weighted images raises the possibility of malignancy. The high signal intensity of pleomorphic adenoma on T2-weighted images is attributed to myxoid tissue within the tumor. In addition, pleomorphic adenomas usually show homogeneous enhancement following gadolinium administration, although heterogeneous enhancement may be observed in large lesions or cystic tumors (9).

Warthin's tumors typically show complex lesions on T1- and T2-weighted images, containing areas that are solid and cystic. The cystic foci appear as areas of high signal intensity on T2-weighted images. Unlike pleomorphic adenomas, Warthin's tumors lack enhancement following gadolinium administration. Nuclear scintigraphy may be useful in diagnosing Warthin's tumor and oncocytoma. These neoplasms are unique in that they show increased isotope uptake on 99m technetium (Tc) scintigraphic studies (10). Nonneoplastic cystic lesions commonly have high signal intensity on T2-weighted images.

High-grade malignancies tend to have irregular margins along the glandular parenchyma and/or

infiltration into the adjacent extraglandular spaces, which can be detected by both MRI and CT. Color Doppler ultrasound may also be useful, as malignant salivary gland neoplasms frequently show a higher grade of vascularity compared with benign neoplasms (11). Positron emission tomography can be used to diagnose and plan treatment of salivary gland malignancies by detecting lymph node metastases and/or distant metastases.

Ultrasound or CT is the examination of choice in patients with inflammatory salivary gland diseases (12). Plain radiography is still a helpful method to diagnose sialolithiasis; 90% of submandibular stones are radiopaque, while most parotid stones are radiolucent. Ultrasound and CT also easily detect calcified stones. The latter is often the best initial study for the evaluation to identify the calculi in the gland. On ultrasound, sialolithiasis is always hyperechogenic enclosed in a hypoechogenic halo representing the dilation of the duct. However, ultrasound is less accurate than CT in distinguishing multiple clusters of stones from single large stones. Sialography is contraindicated in the acute setting of sialadenitis because of the possibility of exacerbating the symptoms associated with the infection.

Conventional and/or MR sialography are useful in staging Sjögren's syndrome, since patients' symptoms may not correlate well with severity of the disease. On conventional sialography, the gland texture of patients with Sjögren's syndrome becomes heterogeneous and reticulated, and multiple cysts may also be observed corresponding with sialectatic changes. MR sialography may replace conventional sialography because MR sialography has the advantage of not requiring cannulation of the duct (13,14). Salivary glands in patients with Sjögren's syndrome show punctate, globular, and destructive patterns by MR sialography. However, in most cases, the diagnosis of Sjögren's syndrome is clinically based on the sicca syndrome, association with other connective tissue disorders, serology of anti-nuclear antibodies, and a lip biopsy.

Fine-Needle Aspiration Cytology

Since major salivary glands are superficially located and easily accessible organs, they are optimal targets for fine-needle aspiration cytology (FNAC). This is a quick, minimally invasive, and technically simple procedure that can be performed in any outpatient setting. However, there are some controversies about the use of FNAC in the diagnosis of salivary gland tumors. The issues include rare but potentially serious complications arising from the procedure, such as tumor seeding along the needle tract, tumor dissemination, injury to the seventh cranial nerve and hemorrhage. In addition, the FNAC procedure itself can induce traumatic tissue injury and infarcts, causing reactive pseudomalignant changes, which may be misdiagnosed as malignant (1). Despite these misgivings, it has been shown that FNAC of the salivary gland lesions is a basically safe and effective diagnostic technique (1,2). Thus, FNAC has gained wide acceptance as a first-line diagnostic procedure and is

widely used among clinicians and pathologists in the diagnosis of salivary gland tumors. The main purposes of FNAC of the salivary gland lesions are to determine whether a process is inflammatory or neoplastic; is benign or malignant; represents a carcinoma or a malignant lymphoma; to render a specific diagnosis, if possible (3). In about one-third of cases, unnecessary surgery can be avoided by means of FNAC diagnosis, especially when the lesions are inflammatory, lymphoproliferative disease including malignant lymphoma, generalized disease, or metastasis to a salivary gland or adjacent lymph node (1,3).

FNAC of salivary gland tumors can be challenging. Factors causing diagnostic difficulties in cytopathologic evaluation of salivary gland neoplasms include diverse cytomorphology, scanty structural information as to cell to cell or cell to stromal component, sampling problems, and the infrequency of many tumor types resulting in limited experience and lack of familiarity by cytotechnologists and pathologists. The salivary gland tumors are unique in their histologic complexity and morphologic variability, reflecting in the cytologic material. While architecture and circumscription are frequently helpful in the histopathologic differential diagnosis of salivary gland neoplasms, these clues are usually lacking in cytologic preparations. If necessary, a cell block is prepared from cells entrapped in a blood clot or tiny tissue particles obtained by FNAC. The cell block enables the pathologist to examine the tissue like a biopsy, and multiple sections can be obtained from paraffin-embedded material for immunohistochemical study. The cytologic examination is very limited because the needle targets only a small area of the neoplasm. The sampled area in an aspiration biopsy may represent only one of the patterns if a given neoplasm shows diverse morphology.

Because of the relatively high false-negative rate, ranging from 5% to 48% in the literature, treatment and follow-up of patients with salivary gland tumors should not be based on FNAC results alone (2,4-6). Negative FNAC findings alone should not prevent surgical intervention when it is otherwise clinically indicated. Fine-needle aspiration cytology combined with careful clinical examinations and imaging studies can lead to correct diagnosis and may help avoid unnecessary surgery. False-negative results can be attributed to various factors including the quality and quantity of FNAC material and sampling errors. Ultrasonographic or CT guidance may help reduce these problems.

Generally, FNAC is considered to have high sensitivity and specificity in detecting salivary gland lesions (2,4-9). The diagnostic sensitivity and specificity for neoplastic or nonneoplastic lesions have been reported as 62% to 98% and 85% to 100%, respectively (2). The reported overall accuracy rate of FNAC in establishing a diagnosis as benign or malignant has been reported to be from 81% to 100% (2,3,6). However, the rate of a correct specific diagnosis falls into the range from 48% to 75% (1,6). The benign lesions that are most often misdiagnosed as malignant are basal cell adenoma, intraparotid lymph node, oncocytoma, and

granulomatous sialadenitis (6). The malignant lesions that are most frequently misdiagnosed as benign are lymphoma, acinic cell carcinoma, low-grade mucoepidermoid carcinoma, adenoid cystic carcinoma, and polymorphous low-grade adenocarcinoma.

Since many benign and malignant salivary gland tumors share similar or overlapping cytologic features, FNAC may occasionally suffer from certain pitfalls in the diagnosis of these tumors (6,9,10). The most common difficulty in FNAC is the distinction of benign neoplasms, such as cellular pleomorphic adenoma, basal cell adenoma, and myoepithelioma, from malignant neoplasms, such as polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma. These lesions have very similar nuclear features of relatively small, bland, nuclei of the epithelial and/or myoepithelial-type cells and basement membrane-like stromal material. The distinction between different subtypes of pleomorphic adenoma, basal cell adenoma, and myoepithelioma is not critical, as the clinical management is identical and the clinical course is benign. However, it is especially important for proper surgical management to distinguish adenoid cystic carcinoma from the other lesions in this group because adenoid cystic carcinomas often require more radical treatment. Other common diagnostic dilemmas in salivary gland FNAC include mucoepidermoid carcinoma versus reactive processes, such as necrotizing sialometaplasia and chronic sialadenitis with squamous or goblet cell metaplasia of the salivary ductal epithelial cells and acinic cell carcinoma versus normal salivary gland acinar cells.

Frozen Section Diagnosis

Preoperative imaging examinations, such as ultrasound, CT, and MRI, are frequently employed to characterize a salivary gland lesion before surgery. However, while certain imaging features can favor or suggest a diagnosis of malignancy, they are often not sufficiently characteristic or reliable to make a specific diagnosis. FNAC has also been widely used for assessing salivary gland lesions preoperatively. Although high sensitivity and specificity of the procedure are reported, there are some controversies regarding the accuracy in the diagnosis of salivary gland tumors, especially that of malignant lesions. Histologic diagnosis of the major salivary gland lesions by incisional biopsy is generally contraindicated because of the possibility of facial nerve injury and tumor seeding. On the other hand, frozen section diagnosis is a potentially useful modality for the surgical management of salivary gland lesions (1-7). The role of frozen section diagnosis of salivary gland lesions is to provide information that would influence immediate surgical treatment. When the preoperative diagnosis is disputed, frozen section diagnosis is often requested to determine whether the lesion is benign or malignant. If the lesion is malignant, frozen section diagnosis is recommended to establish the exact type of malignancy. Frozen section diagnosis is also performed to examine the extent of tumors, status of resection margins, and the involvement of lymph nodes.

Frozen section diagnosis depends on both the ability of the pathologist to give an accurate histologic diagnosis and the experience of the surgeon to interpret the results and provide optimal surgical therapy. Although frozen section diagnosis of salivary gland neoplasia frequently is challenging for the general pathologist, it is reported to be highly reliable in differentiating between benign and malignant diseases. According to a review of 2460 frozen section diagnoses from 24 series, an overall accuracy rate for identifying lesions as a benign or malignant, excluding deferred diagnoses, was 96.3% (2). However, frozen section diagnosis for malignant salivary gland tumors is more difficult and less accurate than for benign tumors, the accuracy rate for benign and malignant tumors being 98.7% and 85.9%, respectively. Therefore, a therapeutic decision should never be made on the basis of a frozen section diagnosis alone, but always in conjunction with the clinical findings. False-positive rates (benign tumors initially diagnosed as malignant) and false-negative rates (malignant tumors initially diagnosed as benign) were 1.1% and 2.6%, respectively.

The most common benign tumor overdiagnosed as malignant was pleomorphic adenoma, which was frequently misdiagnosed as mucoepidermoid carcinoma or adenoid cystic carcinoma (2). Oncocytoma, basal cell adenoma, Warthin's tumor, lymphoepithelial sialadenitis, lymphoepithelial cyst, and sarcoidosis have also caused difficulty. On the other hand, mucoepidermoid carcinoma was the tumor most commonly involved in false-negative diagnosis, followed by acinic cell carcinoma, adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, and malignant lymphoma. Chronic sialadenitis and necrotizing sialometaplasia were most important in the differential diagnosis for mucoepidermoid carcinoma (1).

The main reason for the false-negative errors is inadequate sampling, by either the surgeon or by the pathologist (2). Sampling errors can be minimized if the pathologists receive and examine the entire specimen. Since several types of salivary gland malignancy can be identified only on the basis of their invasive nature rather than cellular or architectural features, frozen sections should always include the neoplasm, tumor capsule if present, and surrounding salivary gland tissue and/or soft tissue to evaluate tumor circumscription as possible. Sampling should never be limited to the middle of the tumor. Benign tumors with multinodularity, such as recurrent pleomorphic adenoma, oncocytoma, the membranous type of basal cell adenoma, and canalicular adenoma, must not be misinterpreted as malignancy.

Finally, if a definite diagnosis cannot be made by frozen section assessment, further surgery should be deferred until a final histopathologic diagnosis on permanent sections is obtained (1). However, the surgeon often has immediate need of the information whether the tumor is benign or malignant. Close discussion between the pathologist and surgeon is essential to reach an accurate diagnosis and to prevent any unnecessary extensive surgery.

Genetics

Recent molecular genetic studies have provided important information on genetic and epigenetic alterations in salivary gland tumors, especially on implications of their tumorigenesis, differential diagnosis, and therapeutic strategies (1,2).

Specific chromosomal translocations have been reported in pleomorphic adenomas and mucoepidermoid carcinomas. In approximately 70% of cases of pleomorphic adenoma, cytogenetic aberrations can be demonstrated in one of the following three patterns: (i) chromosomal rearrangement of 8q12 (39% of cases), such as t(3;8)(p21;q12), t(5;8)(p13;q12); (ii) chromosomal rearrangement of 12q13–15 (8% of cases), such as t(9;12)(p24;q14–15), ins(9;12)(p24;q12q15); (iii) sporadic, clonal changes not involving 8q21 or 12q13–15 (23% of cases) (3,4). The target gene in pleomorphic adenomas with 8q12 abnormalities is *PLAG1* (pleomorphic adenoma gene 1), which is a developmentally regulated zinc finger gene (5). The partner genes include *CTNNB1* (β -catenin) in t(3;8)(p21;q12) (5), *LIFR* (leukemia inhibitory factor receptor) in t(5;8)(p13;q12) (6), and *SII* (transcription elongation factor SII) in a cryptic translocation (7). Fusion products *CHCHD7-PLAG1* or *TCEA1-PLAG1* can also occur resulting from cryptic, intrachromosomal 8q rearrangements (8). Translocations involving 8q12 result in promoter swapping between *PLAG1* and a ubiquitously expressed translocation partner gene, leading to ectopic *PLAG1* over-expression and reduced expression of the partner gene (5–8). The *PLAG1* protein is a nuclear oncoprotein that functions as a DNA-binding transcription factor, which has been postulated to play an important role in the oncogenesis of pleomorphic adenomas (9,10). This was established by microarray analysis, which indicated that the oncogenic capability of *PLAG1* is mediated, at least partly, by the IGF-II mitogenic signaling pathway (9). However, oncogenic activation of *PLAG1* itself is also a crucial event in other human tumors, including lipoblastoma, hepatoblastoma, and acute myeloid leukemia (10).

The target gene in pleomorphic adenomas with rearrangements on chromosome 12q13–15 is the high-mobility group protein gene, *HMGA2* (previously known as *HMGIC*). The partner genes are *FHIT* (fragile histidine triad gene) in t(3;12)(p14.2;q14–15) (11), *NFIB* (nuclear protein involved in transcriptional regulation) in ins(9;12)(p23;q12q15) (12), and *WIF1* (*Wnt* inhibitory factor 1) (13). The gene fusion results in separation of the DNA-binding domains from potential mRNA-destabilizing motifs, leading to deregulation of *HMGA2* expression. The *HMGA2* protein acts as an architectural transcription factor that promotes activation of gene expression by modulating the conformation of DNA (12,13). High-level expression of *HMGA2* resulting from gene amplification was suggested to be of importance for malignant transformation of pleomorphic adenomas (14). Cytogenetic abnormalities on 12q14 involving the *HMGA2* gene can also be identified in other variety of benign and malignant tumors as well, such as lipomas, uterine

leiomyomas, and myeloid malignancies (15). However, because the *PLAG1*- or *HMGA2*-containing fusion genes described above have so far been identified only in pleomorphic adenomas, their detection using reverse transcriptase-polymerase chain reaction or fluorescence in situ hybridization may be potentially useful in cases of difficult differential diagnoses.

In mucoepidermoid carcinomas, a specific chromosomal translocation, t(11;19)(q21;p13), which creates a fusion transcript of *MECT1* (mucoepidermoid carcinoma translocated-1) at 19p13 with *MAML2* (mastermind-like gene family) at 11q21, has been found in up to 70% of cases (16–18). The *MECT1-MAML2* fusion transcript acts as a coactivator for Notch receptor transcriptional activation and signalling (19). This translocation is frequently associated with a low-grade histology, and the presence of the transcript appears as an independent prognostic factor of mucoepidermoid carcinoma (16,17). Recently, a fusion between *EWSR1* and *POU5F1* has also been reported in a single case of high-grade mucoepidermoid carcinoma with the translocation, t(6;22)(p21;q12) (20). These fusion transcripts can potentially be utilized to establish the diagnosis and expected to be useful in the development of novel molecular therapeutic strategies for mucoepidermoid carcinoma.

The most frequent cytogenetic aberrations in adenoid cystic carcinomas involve chromosomes 6q, 9p, 12q, 17p, and 19q regions (21). Loss of heterozygosity at 6q 23–25 correlated with histologic grade and clinical behavior in this tumor (22). On the other hand, in one study of 25 acinic cell carcinomas, 84% of the tumors had alteration in at least one of the 20 chromosomal loci on 1, 4, 5, 6, and 17, most frequently at chromosomes 4p, 5q, 6p, and 17p regions (23). Concurrent analysis of the benign and malignant components of carcinoma ex pleomorphic adenoma showed alterations of chromosome 8q and/or 12q in both components and additional alterations in 17p only in the carcinoma (24). The same cytogenetic abnormality in the chromosome 16q12–13 region, the *CYLD* (cylindromatosis gene) between dermal cylindromas, and membranous basal cell adenomas has been reported in two familial cases (25).

Mutation and over-expression of p53 are found in a relatively high proportion of high-grade salivary gland carcinomas, such as salivary duct carcinoma, carcinoma ex pleomorphic adenoma, large cell carcinoma, dedifferentiated carcinoma, and hybrid carcinoma. Salivary duct carcinomas are usually distinctly positive for HER-2/*neu* protein with or without the gene amplification by means of fluorescence in situ hybridization (26–28).

Oligonucleotide microarray analysis identified several genes that were associated with adenoid cystic carcinoma (29). The most overexpressed genes encoded by adenoid cystic carcinoma included basement membrane and extracellular matrix proteins of myoepithelial differentiation, such as laminin- β 1, versican, biglycan (*BGN*), and type IV collagen- α 1. Other genes, which were highly expressed in adenoid cystic carcinoma compared with the other carcinomas,

included transcription factors *SOX-4* and *AP-2* family, and members of the *Wnt/β-catenin* signaling pathway, such as *casein kinase 1*, *epsilon*, and *frizzled-7*. Comparative gene expression profiles were studied in mucoepidermoid carcinoma, acinic cell carcinoma, and salivary duct carcinoma (30). Only 5 out of 162 genes were overexpressed in all carcinomas, including fibronectin 1 (*FN1*), tissue metalloproteinase inhibitor 1 (*TIMP1*), *BGN*, tenascin-C (*HXB*), and insulin-like growth factor binding protein 5 (*IGFBP5*), whereas 16 genes, which are related to cell-cycle proteins, proteins of signal transduction and translation, were underexpressed. Other microarray studies demonstrated differential gene expression profiles in pleomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, acinic cell carcinoma, and salivary duct carcinoma (31).

Methylation is one of the epigenetic modifications that play an important role in the transcriptional inactivation of tumor suppressor genes in human cancer. Recent methylation studies revealed that methylation in promoter regions at *E-cadherin* gene has been often identified in adenoid cystic carcinomas (32,33). Also, in adenoid cystic carcinomas, frequent promoter methylation was found in cyclin-dependent kinase inhibitors genes; such as *p15*, *p16INK4a*, *p18*, *p19*, and *p21*; ras-association domain isoform A (*RASSF1A*); and the death-associated protein kinase (*DAPK*) (34,35). About one-third of mucoepidermoid carcinomas showed methylation of the *p16INK4a* gene-promoter region (36). High percentage of methylation occurred at *RASSF1* and retinoic acid receptor β2 (*RARβ2*) genes in salivary duct and acinic cell carcinomas (37). Furthermore, relatively high frequency of promoter methylation in tumor suppressor gene *RB1* was detected in salivary gland carcinomas (38).

Classification

Salivary gland tumors can show a strikingly diverse range of histomorphologic differentiation and architectural configurations. This has led to a plethora of individual tumor types and a frequently changing terminology. In addition, this variability is seen within many of these tumor entities, each of which may have several named subtypes. Classification is further complicated by the presence of dedifferentiated and hybrid tumors. As emphasized by Ellis and Auclair (1), the classification of salivary tumors, as with any other type of neoplasm, is a dynamic rather than a static process. Any tendency to regard a classification as immutable should be firmly resisted. Formal classifications merely represent the consensus of a group of individuals at a given moment in time. In this chapter we will follow closely the classification proposed by the World Health Organization (WHO) in 2005 (Table 4) (2). However, several entities, including keratocystoma and sialolipoma, that were not included in the WHO classification will be discussed to broaden awareness and promote discussion. In addition, we have included sections on intraosseous (central) and hybrid tumors.

Table 4 WHO Histologic Classification of Tumors of the Salivary Glands, 2005

Malignant epithelial tumors	Benign epithelial tumors
Acinic cell carcinoma	Pleomorphic adenoma
Mucoepidermoid carcinoma	Myoepithelioma
Adenoid cystic carcinoma	Basal cell adenoma
Polymorphous low-grade adenocarcinoma	Warthin's tumor
Epithelial-myoepithelial carcinoma	Oncocytoma
Clear cell carcinoma, not otherwise specified	Canalicular adenoma
Basal cell adenocarcinoma	Sebaceous adenoma
Sebaceous carcinoma	Lymphadenoma
Sebaceous lymphadenocarcinoma	Sebaceous
Cystadenocarcinoma	Nonsebaceous
LGCCC	Ductal papillomas
Mucinous adenocarcinoma	Inverted ductal papilloma
Oncocytic carcinoma	Intraductal papilloma
Salivary duct carcinoma	Sialadenoma
Adenocarcinoma, not otherwise specified	papilliferum
Myoepithelial carcinoma	Cystadenoma
Carcinoma ex pleomorphic adenoma	Soft tissue tumors
Carcinosarcoma	Haemangioma
Metastasizing pleomorphic adenoma	Hematolymphoid tumors
Squamous cell carcinoma	Hodgkin's lymphoma
Small cell carcinoma	Diffuse large B-cell lymphoma
Large cell carcinoma	Extranodal marginal zone-B cell lymphoma
Lymphoepithelial carcinoma	Secondary tumors
Sialoblastoma	

Abbreviation: LGCCC, Low-grade cribriform cystadenocarcinoma.

Staging

The TNM Classification only applies to carcinomas of the major salivary glands: parotid (C07.9), submandibular (C08.0), and sublingual (C08.1) glands (1, 2, 3). Tumors arising in minor salivary (mucus-secreting glands in the lining membrane of the upper aerodigestive tract) are not included in this classification but at their anatomic site of origin. There should be anatomical confirmation of the disease. The regional lymph nodes are the cervical nodes. The TNM Clinical Classification of salivary gland tumors is shown in Table 5.

H. Benign Tumors

Pleomorphic Adenoma

Introduction. Pleomorphic adenoma has been defined as “a tumor of variable capsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial and modified myoepithelial elements intermingle most commonly with tissue of mucoid, myxoid or chondroid

Table 5 TNM classification of carcinomas of the salivary gland**T – Primary tumour**

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumour more than 4 cm and/or tumour with extraparenchymal extension*
T4a	Tumour invades skin, mandible, ear canal, or facial nerve
T4b	Tumour invades base of skull, pterygoid plates, or encases carotid artery

Note: *Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues or nerve, except those listed under T4a and 4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

N – Regional lymph nodes[#]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Note: Midline nodes are considered ipsilateral nodes.

M–Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV A	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IV B	T4b	Any N	M0
	Any T	N3	M0
Stage IV C	Any T	Any N	M1

[#]The regional lymph nodes at the cervical nodes.

appearances'' (1). Synonyms include mixed tumor and benign mixed tumor.

Clinical features. Pleomorphic adenoma is the most common salivary neoplasm and accounts for 60% to 70% of all parotid tumors, 40% to 60% of submandibular tumors, and 40% to 70% of all minor salivary neoplasia (2–6). There is an annual incidence rate of approximately 2.4 to 3.05 per 100,000 persons (7,8). Pleomorphic adenoma can also arise in the nasal cavity, paranasal sinuses, and larynx (9–11). The mean age at presentation is 46 years (2), but cases occur over a wide age range and can occasionally be seen in young children (6,12). Some studies have shown a bimodal age distribution (13). There is a female preponderance of 1.9:1 (6). Familial cases of pleomorphic adenoma are rare, with only four case reports in the literature (14–17). The large majority (~80%) of tumors arise in the parotid gland, with most of the remainder involving the submandibular gland (~10%) and minor seromucous glands (~10%). Pleomorphic adenomas of the sublingual gland are exceptionally rare (18). Parotid tumors usually arise within the superficial lobe, especially its lower pole, but 10% may occur in the deep lobe, or from an

accessory parotid gland. The most common minor salivary gland sites are the palate, lip, and buccal mucosa. Pleomorphic adenomas have been reported in a wide variety of other sites, including cervical lymph nodes, mandible, lung, breast, pituitary fossa, lacrimal gland and sac, ear, and lung (19–27). Histologically similar tumors in the skin are termed "chondroid syringomas." Pleomorphic adenoma may show a synchronous or metachronous association with other salivary neoplasms, particularly Warthin's tumors, in the same or other glands (12).

Pleomorphic adenoma in the major glands usually presents as a slow-growing, painless mass. Small tumors typically form smooth, firm, and mobile lumps, but larger tumors tend to be bosselated and may attenuate and discolor the overlying skin. Deep-lobe parotid tumors may present as an intraoral or parapharyngeal mass (28). Pain or facial nerve palsy may occasionally be seen in tumors that are infected or have infarcted. Pleomorphic adenomas of the minor salivary glands usually present as painless, submucosal swellings. The most common site is the junction of the hard and soft palate unilaterally, and here the tumors are often adherent to the adjacent mucoperiosteum.

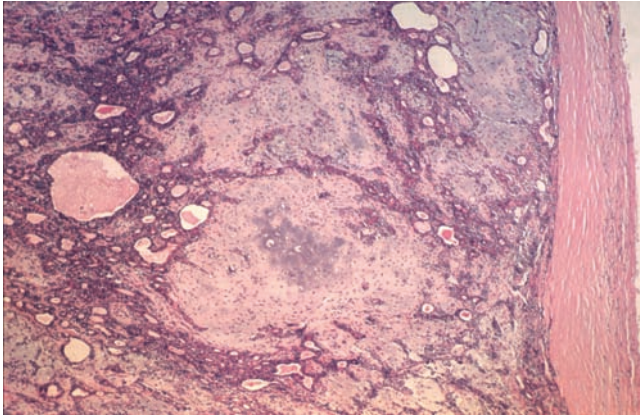


Figure 39 Pleomorphic adenoma showing a discrete fibrous capsule, cartilage, and duct-like structures.

Most pleomorphic adenomas range from 2 to 6 cm in greatest diameter, but some tumors are massive (29).

Pathology. Grossly, pleomorphic adenomas are usually solitary, well-defined, ovoid or round masses. Larger neoplasms may have a characteristic bosselated surface. Their consistency varies from hard to rubbery or soft and fluctuant. The cut surface of the tumor is characteristically solid and the color varies from gray-blue, pale yellow to tan. There may be gritty areas, and gelatinous or glistening foci may be present when there is cartilaginous or myxochondroid differentiation. Necrotic or cystic regions may be a feature of larger tumors. Recurrent tumors appear as multifocal soft tissue masses that may be widely dispersed.

Most tumors are encapsulated, but there is wide variation in both the thickness and presence of the capsule (Fig. 39). There may be a complete lack of capsule, especially in predominantly mucoid tumors. In many tumors there is a distinct tendency for the tumor to split away from the overlying capsule when handling the specimen. This may be a factor in producing an illusory plane of cleavage during surgery. Nodules of tumor may bulge through the capsule and give a false impression of multifocality in some planes of section (Fig. 40). The capsule in minor gland pleomorphic adenomas is often poorly formed or absent.

Pleomorphic adenomas are characterized by a remarkable degree of morphologic diversity between individual tumors and often within a single tumor mass. The most important histologic components of the tumor are the capsule, the epithelial and modified myoepithelial cells, and the mesenchymal or stromal elements. There is evidence using a HUMARA assay that the epithelial and stromal cells of pleomorphic adenoma have a common origin (30).

The capsule varies in both thickness and presence. A quantitative study showed the capsular thickness ranging from 15 to 1750 μm (31). In predominantly mucoid tumors, there are usually areas where the capsule is virtually absent and the tumor then abuts onto adjacent normal salivary parenchyma or fat.

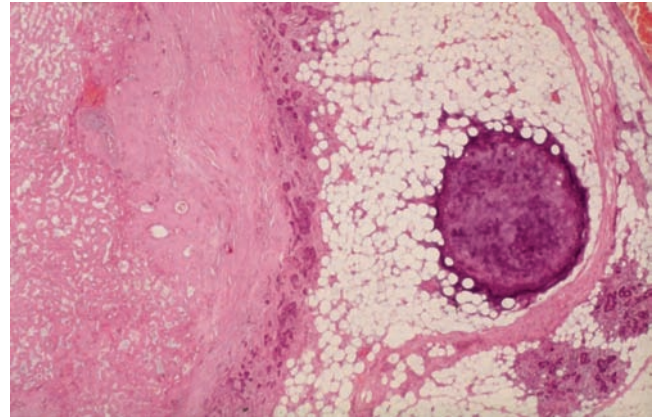


Figure 40 Pleomorphic adenoma showing "satellite" nodule that is typically attached to the main tumor mass.

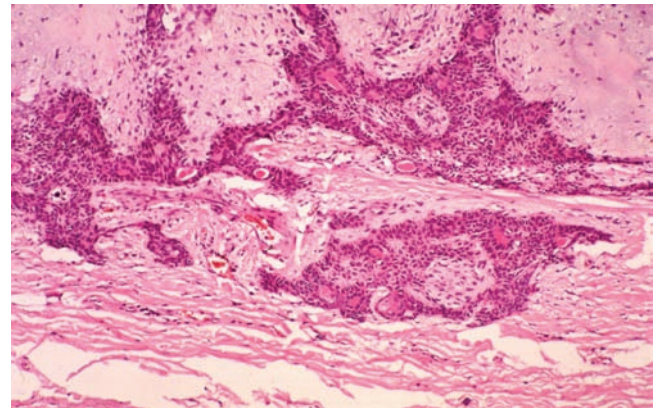


Figure 41 Pleomorphic adenoma showing capsular invasion.

Many tumors show local extension of fingerlike processes into the capsule (Fig. 41). Tumor may also bulge through the capsule and form pseudosatellite nodules. This is also particularly common in predominantly myxoid tumors. Serial sectioning has shown that these nodules are invariably attached by an isthmus to the main tumor mass (32,33). Microscopically, it can be shown that the macroscopic parallel clefts seen between the tumor and capsule are, in fact, within the tumor itself, leaving tumor cells attached to the capsular wall. Minor salivary gland pleomorphic adenomas characteristically lack encapsulation and may incorporate normal host tissue as they expand, giving a false impression of invasion.

The epithelial component of pleomorphic adenomas shows a wide variety of cell types, including cuboidal, basaloid, and squamous, and the myoepithelial cells may be spindle cell, plasmacytoid, or clear. Rarely, mucous, sebaceous, or serous acinar cells are also present. The epithelium can form sheets,

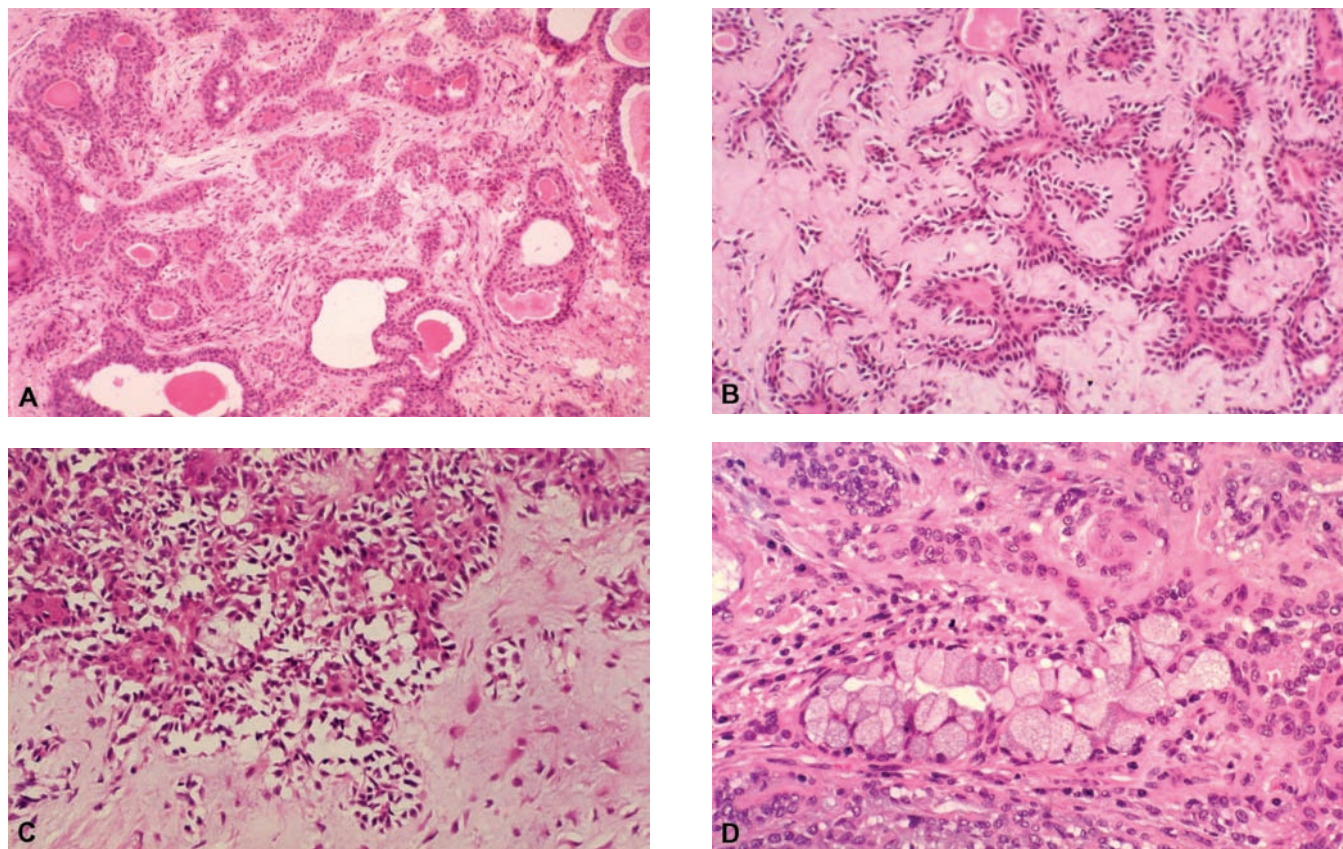


Figure 42 (A) Duct-like structures in fibromucinous stroma. (B) Double-layered duct-like structures with a conspicuous abluminal layer of clear myoepithelial cells. (C) Sheets of epithelioid and clear myoepithelial cells in mucoid stroma. (D) Pleomorphic adenoma showing a focus of mucous metaplasia.

cords, or ductal structures (Fig. 42). The latter are composed of an inner layer of cytologically bland, large, cuboidal cells with vacuolated nuclei without prominent nucleoli, surrounded by an outer layer of myoepithelial cells. The myoepithelial cells may be morphologically similar to the duct lining cells or have variably eosinophilic to clear cytoplasm and condensed, small, hyperchromatic nuclei, which are flattened or triangular. The ducts may contain eosinophilic secretory material and, although usually small, they may become distended to form microcysts. More solid areas of epithelial cells lacking ductal lumina may be seen admixed with myoepithelial cells. There can be moderate degrees of nuclear atypia and an increased mitotic frequency, particularly in dense, cellular foci. Occasionally tumors contain multinucleated and other bizarre neoplastic cells (34). This finding does not appear to have any prognostic significance. Crystalloids, including collagenous material, tyrosine-rich crystals, which form flowerlike ("daisy head") structures (Fig. 43A,B), and oxalate-like crystals, may be present (6). Intraductal, concentrically laminated, corpora amylacea-like condensations (Fig. 43C), and stromal amyloid are occasional features (35). The mesenchymal component, which

may be myxoid, cartilaginous, or hyalinized, is a product of the modified myoepithelial cells. These cells have a wide range of appearances, which includes polygonal, plasmacytoid (hyaline cell), spindle-shaped, or clear cell (Fig. 44) (36). Polygonal cells may have a fine reticular arrangement, and a prominent spindle cell component can occasionally display a schwannoma-like palisading growth pattern. Plasmacytoid myoepithelial cells are distinctive round to oval cells with eccentric nuclei and dense eosinophilic cytoplasm. They usually form sheets and small islands within a hyalinized stroma. Plasmacytoid cells have a distinct tendency to separate from one another. Squamous metaplasia, sometimes with keratin pearl formation, is a common feature, which can involve both ducts and sheets of cells (Fig. 45). Extensive areas of squamous metaplasia are uncommon unless there has been surgical intervention or infarction (Fig. 46). Infrequently, tumors have areas of sebaceous metaplasia, clear cell change, and mucoepidermoid-like metaplasia. Focal oncocytosis is relatively common but occasionally the entire tumor can be affected, making diagnosis difficult (Fig. 47) (37,38).

The mesenchymal component is myxoid, cartilaginous, or hyalinized and sometimes forms the

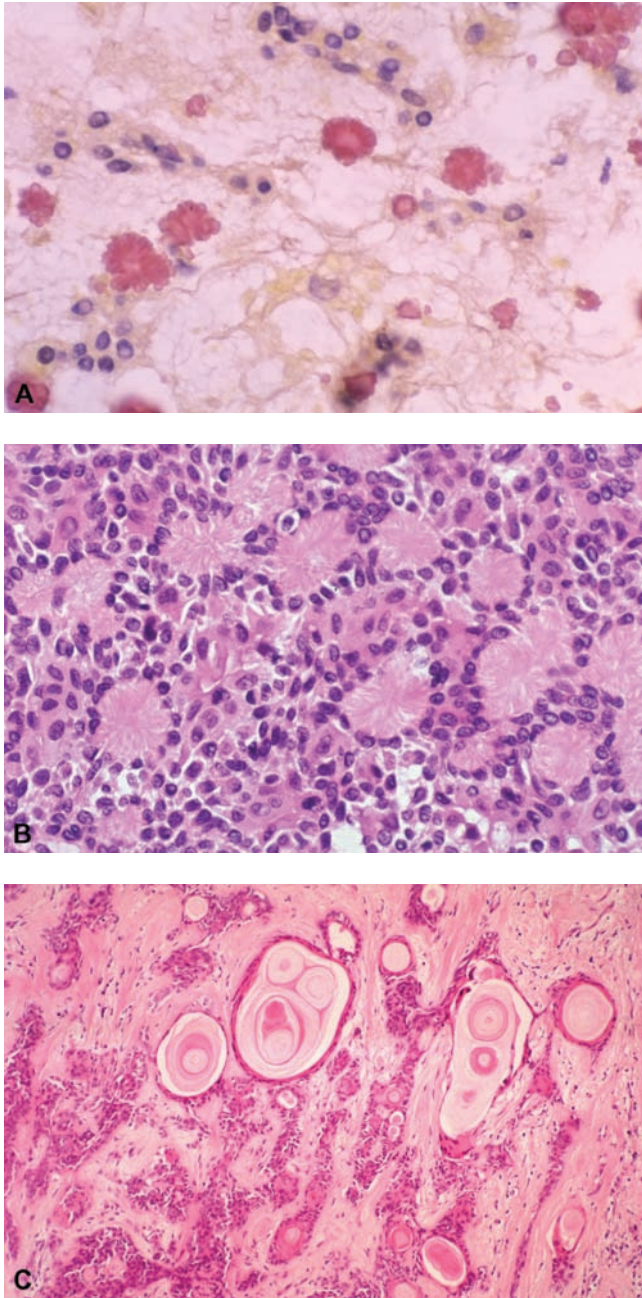


Figure 43 (A) Tyrosine crystals in characteristic "daisy-head" pattern. Mayer's hemalum and tartrazine stain. (B) Collagenous crystalloids. (C) Pleomorphic adenoma showing intraductal corpora amylacea-like condensations.

predominant element of the tumor. Cells within the myxoid areas are myoepithelial in origin and their cellular periphery tends to blend into the surrounding stroma. The cartilage-like material has similar biochemical properties to true cartilage and is positive for both type II collagen and keratan sulfate (Fig. 48A). Bone may form directly by stromal osseous metaplasia or, more rarely, by a process similar to endochondral

ossification (Fig. 48B,C). Some tumors show deposition of eosinophilic, hyaline material within islands of tumor cells and within the stroma. The material is positive with collagen and elastin stains, and in some cases it can form the bulk of the tumor. It can attenuate the epithelial elements to give a cylindromatous or cribriform appearance that can be mistaken for adenoid cystic carcinoma (Fig. 48D). Some tumors show progressive scarring with destruction and loss of much of the epithelial component. It is important to examine such tumors closely for residual epithelial elements, as there is a higher risk of malignant progression in these old, scarred pleomorphic adenomas. In a study of 65 pleomorphic adenomas, 9 tumors (13.8%) showed malignant progression (39). It was found that a prominent hyalinized stroma correlated ($p < 0.5$) with malignant progression. Fat cells are common in the stroma of pleomorphic adenoma, particularly in minor glands. Tumors that have a lipomatous stromal component of 90% or more have been called lipomatous pleomorphic adenomas (40,41), and a myxolipomatous variant has been described (Fig. 49) (42).

There can be significant variations in the cellularity of pleomorphic adenoma, with some tumors being sparsely cellular and composed predominantly of a mucoid component and others consisting of densely packed, solid sheets of epithelial or myoepithelial cells. The latter tumors have been called *cellular pleomorphic adenomas*.

Areas of lymphocytic and plasma cell infiltration are common, even when there has been no previous surgical manipulation (31). They are usually seen in the subcapsular region. Rarely, a lymphoplasmacytic infiltrate appears to virtually destroy the bulk of the epithelial component of the tumor, leaving residual islands resembling those seen in lymphoepithelial lesions. Occasionally there is extensive, acute, and chronic inflammatory infiltration and prominent central necrosis (43). This may be the result of spontaneous infarction or, increasingly, fine-needle aspiration biopsy (44,45). Clinically, these tumors may be symptomless or there can be an episode of sudden pain and rarely facial nerve palsy. Such tumors can occasionally show florid squamous metaplasia that can easily be confused with malignancy (46–49). Occasionally, there is extensive cystic degeneration, with residual tumor forming no more than a cellular rim surrounding a central cystic cavity. Rare, truly multicentric pleomorphic adenomas have been reported (50–52). Exceptionally, multifocal pleomorphic adenoma may be the result of nonsurgical physical injury.

Occasionally, small nests or more solid aggregates of tumor cells can be seen within vascular spaces (Fig. 50). Although these are usually present within the body of the tumor, or close to its periphery, intravascular tumor can sometimes be seen in more distant vessels. This phenomenon appears to be extremely rare in the United States, but it was a feature seen in 8.9% of intraoral pleomorphic adenoma in a report from South Africa (53). This unusual phenomenon does not appear to represent true intravascular invasion and is probably the result of

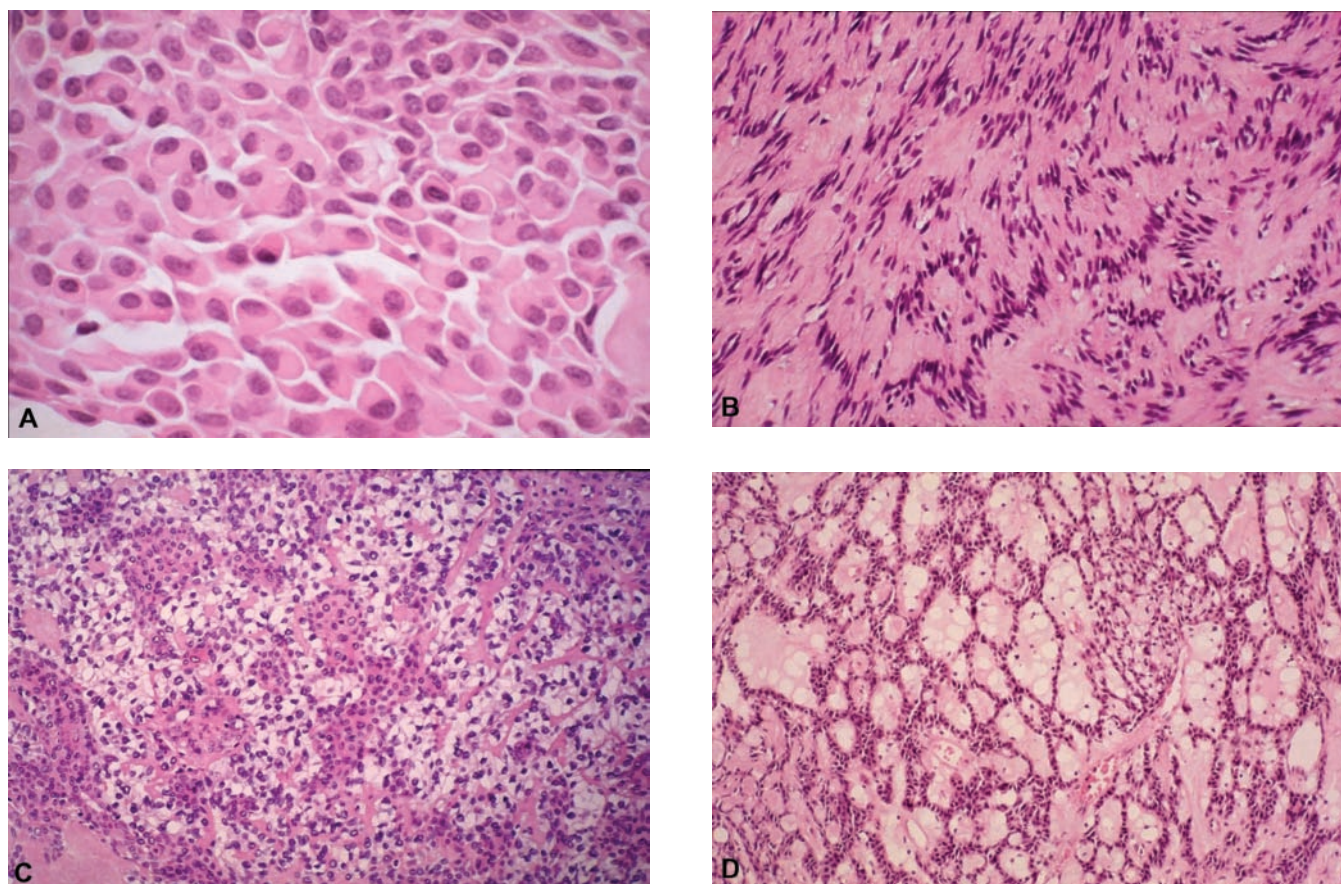


Figure 44 (A) Plasmacytoid (hyaline) myoepithelial cells. (B) Spindle-shaped myoepithelial cells forming a neurilemmoma-like pattern. (C) Numerous clear myoepithelial cells. (D) Myoepithelial cells forming a reticular pattern.

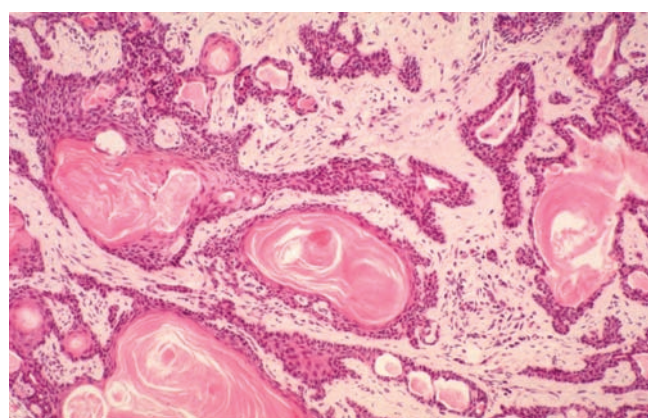


Figure 45 Pleomorphic adenoma showing focal squamous metaplasia.

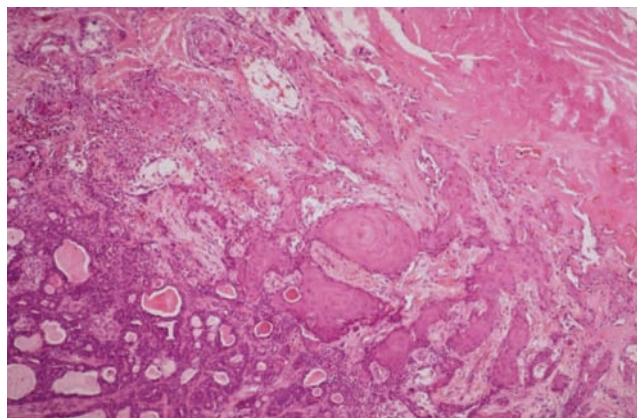


Figure 46 Infarcted pleomorphic adenoma showing florid squamous metaplasia.

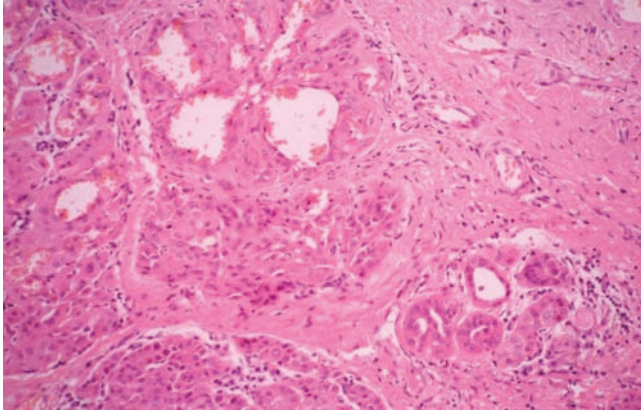


Figure 47 Pleomorphic adenoma showing extensive oncocytic metaplasia.

intraoperative surgical manipulation. It does not seem to have any clinical consequences, including the risk of metastatic disease.

Immunohistochemistry. As with many other salivary gland tumors, the immunocytochemical profile of pleomorphic adenoma is rarely of value in differential diagnosis. However, a number of immunocytochemical studies have given valuable insights into the histogenesis of this unique tumor. The luminal cells of tubuloglandular elements of pleomorphic adenoma are positive for cytokeratins 3, 6, 10, 11, 13, and 16. Modified myoepithelial cells are irregularly positive for cytokeratins 13, 14, and 16 and pan-cytokeratin (54). They are also positive for vimentin, S-100 protein, glial fibrillary acidic protein, α -smooth muscle actin, HHF-35, calponin, and smooth muscle myosin, especially in the myxoid areas and/or in the solid areas (55–58). Tumoral myoepithelial cells are also reactive for p63 (59). There is moderately intense c-kit (CD117) staining in the luminal cells of pleomorphic adenoma

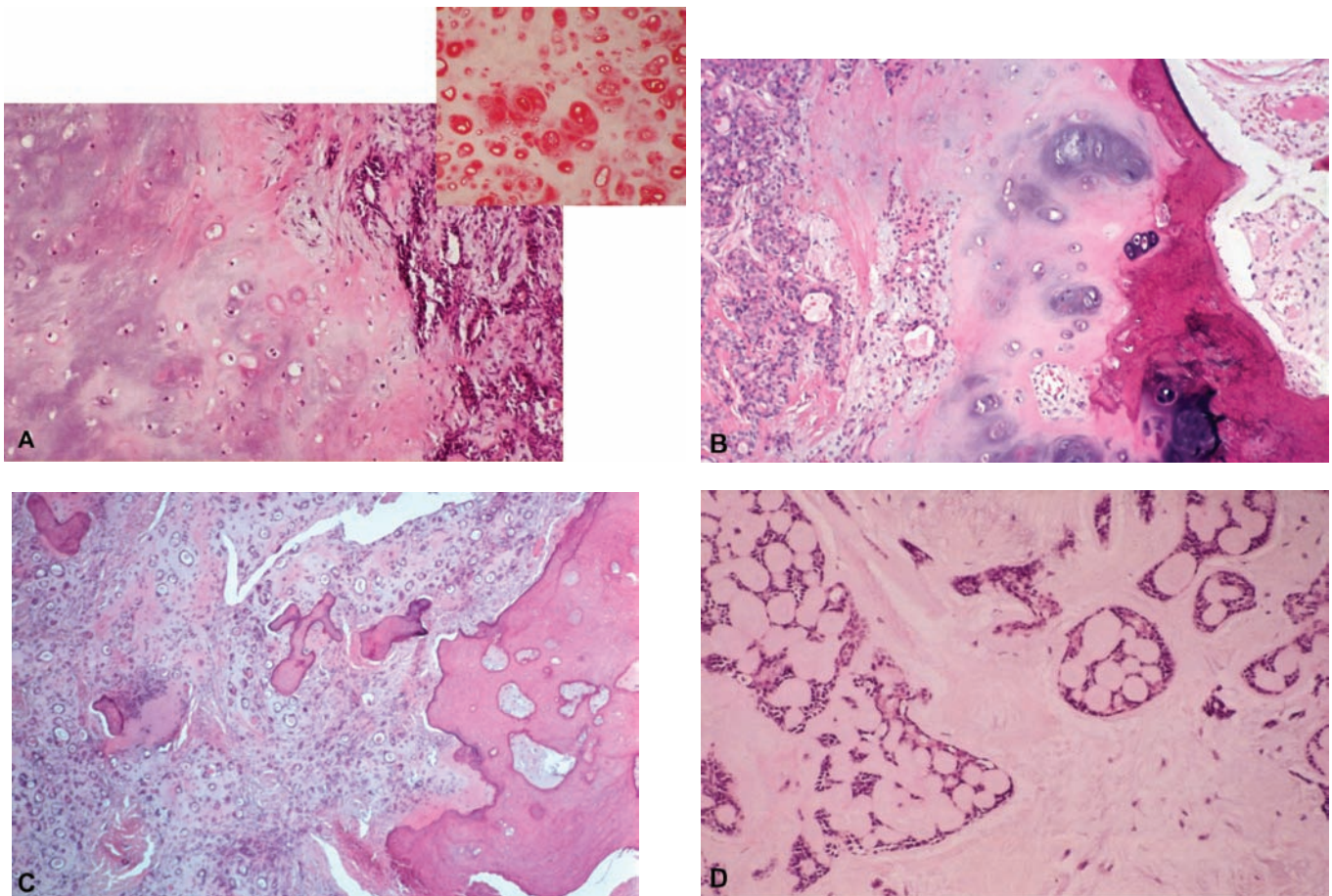


Figure 48 (A) Cartilaginous differentiation. The inset shows staining for keratan sulfate. (B) Pleomorphic adenoma showing bone formation by endochondral ossification. (C) Pleomorphic adenoma showing bone forming by osseous metaplasia in stroma. (D) Pleomorphic adenoma with cribriform areas resembling adenoid cystic carcinoma.

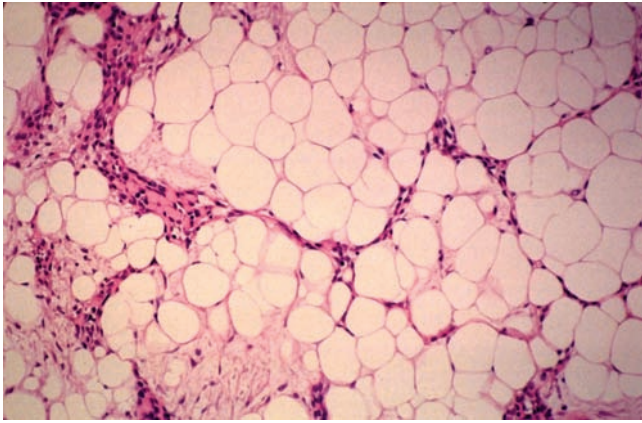


Figure 49 Lipomatous pleomorphic adenoma.

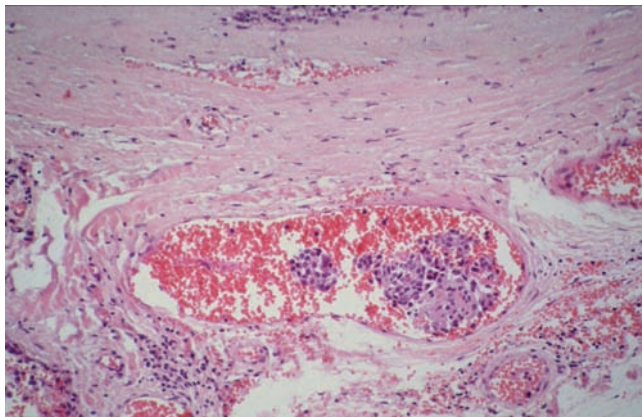


Figure 50 Tumor in a vascular space close to the margin of a pleomorphic adenoma.

(60). The nonlacunar cells in the chondroid areas are positive for both vimentin and pan-cytokeratin, whereas the lacunar cells are positive only for vimentin (61). Lacunar cells in the chondroid areas are also positive for S-100 protein. The modified myoepithelial cells in the myxoid areas and the luminal cells express transforming growth factor (TGF)- β 2, whereas the lacunar cells in the chondroid areas weakly express TGF- β 3 (62). Spindle-shaped myoepithelial cells adjacent to these chondroid areas also express bone morphogenetic protein (BMP) (63), whereas the inner ductal cells and lacuna cells in the chondroid areas express BMP-6 (64). Type II collagen and chondromodulin-1 are present in the chondroid matrix, mirroring the composition of normal cartilage (65).

Molecular-genetic data. About 70% of pleomorphic adenomas show karyotypic abnormalities, and rearrangements involving 8q12–15 (39%), and 12q13–15 are the most common (8%) (66). Secondary chromosomal alterations are seen in about a third of

pleomorphic adenomas with abnormal karyotypes. Patients with karyotypically normal pleomorphic adenomas are reported to be significantly older than those with rearrangements of 8q12 (51.1 vs. 39.3 years, $p < 0.001$). In addition, adenomas with normal karyotypes tend to be more stroma-rich than tumors with 8q12 abnormalities (67).

PLAG1, a developmentally regulated zinc finger gene, appears to be the target gene in pleomorphic adenoma with 8q12 abnormalities (68–70). Translocations involving 8q12 can result in promoter swapping/substitution between *PLAG1* and translocation partner genes such as *CTNNB1-PLAG1* and *LIFR-PLAG1*. This in turn leads to activation of *PLAG1* expression. It has been postulated that deregulation of *PLAG1* target genes, including *IGF2*, may have a significant role in the genesis of pleomorphic adenoma (71). The finding of *PLAG1* rearrangements in cells with both epithelial and myoepithelial phenotypes, reinforces the pluripotent single-cell theory of the histogenesis of pleomorphic adenoma (72).

RAS mutation and activation are common in pleomorphic adenoma, particularly in tumors showing *PLAG1* activation (73,74). However, amplification and/or over-expression of *ERBB2* is rare (75,76), and *TP53* alterations are infrequent in adenomas (76–78). In addition, *TP53*-related genes *TP63* and *TP73*, which are putative myoepithelial markers, are overexpressed in basal and myoepithelial cells in pleomorphic adenomas (59,78).

Pleomorphic adenomas contain SV40 DNA sequences and express the SV40 large T antigen. This suggests that the virus may play a role as a cofactor in the pathogenesis of pleomorphic adenoma (79).

Differential diagnosis. In most cases of surgically excised pleomorphic adenoma the diagnosis is relatively easy as there are characteristic combinations of epithelial and mesenchymal elements. However, particularly when confronted with limited biopsy material from minor salivary glands, the diagnosis can be more challenging. The main differential diagnoses of minor salivary gland pleomorphic adenoma are polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma. Sharply circumscribed cribriform or cylindromatous structures, although characteristic of adenoid cystic carcinoma, can also be seen with polymorphous low-grade adenocarcinoma and pleomorphic adenoma. These tumors may be indistinguishable in limited surgical material. In resection specimens, however, the presence of more typical areas and the absence of features such as infiltration and perineural invasion usually facilitates diagnosis. Pleomorphic adenoma can show double-layered, duct-like structures with an inner layer of dark, cuboidal cells and an outer layer of clear cells. Similar biphasic features may be a feature of the tubular variant of adenoid cystic carcinoma and epithelial-myoepithelial carcinoma. In pleomorphic adenoma and adenoid cystic carcinoma the abluminal clear cells usually have small, hyperchromatic and angular nuclei. Those in epithelial-myoepithelial carcinoma are typically larger and

more vesicular. However, in small biopsies it may not be possible to make a confident distinction between these tumors, and a circumspect report should be considered. In such specimens, the value of c-kit expression in differentiating pleomorphic adenoma from adenoid cystic carcinoma is yet to be established (80).

Squamous cell carcinoma or mucoepidermoid carcinoma may need to be considered in the differential diagnosis, particularly in limited biopsy tissue of a pleomorphic adenoma showing squamous or mucoepidermoid metaplasia. This is especially the case in pleomorphic adenomas of minor glands such as the palate, as tumors in this location can be particularly cellular and often lack cartilaginous or myxoid differentiation. The presence of plasmacytoid myoepithelial cells provides strong support for a diagnosis of pleomorphic adenoma and effectively eliminates the possibility of mucoepidermoid carcinoma and squamous carcinoma.

Treatment and prognosis. The main problems in the clinical management of pleomorphic adenoma are the tendency of tumors to recur following surgery and the risk of malignant transformation. Recurrent tumor is usually multifocal and occasionally becomes inoperable (Fig. 51) (81,82). In addition, treatment of recurrent tumors carries a high risk of facial nerve injury, further recurrences, and an increased risk of malignant progression (80). In pleomorphic adenoma of minor salivary glands recurrences are rare, and most of the problems are seen in tumors of the parotid gland. A meta-analysis of parotid pleomorphic adenoma showed 3.4% of tumors recurred after five years and 6.8% after 10 years (83). Since superficial parotidectomy, either total or partial, became a more widely used treatment, the recurrence rate has usually been less than 5% (84–87). In recent years, more conservative surgical techniques have been adopted in an attempt to avoid the risks of facial nerve palsy and Frey syndrome (88–93). Total parotidectomy with preservation of the facial nerve,

however, may remain necessary for deep-lobe tumors (94). There is a particular tendency for predominantly myxoid pleomorphic adenomas to recur. These tumors are diffuent, have thinner capsules, and nodules of tumor may bulge through the capsule. There is a higher risk of rupture during surgery, and these neoplasms appear to have a greater rate of recurrence than predominantly cellular tumors (81,85). In this context, a recent study showed that expression of the mucin MUC1/DF3 in pleomorphic adenoma was a potential marker of the risk of recurrence (95). Patients with more than one recurrence usually had their first recurrence earlier than patients who were cured after re-excision of their only recurrence (47 vs. 105 months) (83). It appears that recurrences are more likely in young patients (81,96). Radiotherapy has been used to treat recurrences and sometimes following rupture of the tumor during surgery, but its value remains uncertain (97,98).

Myoepithelioma

Introduction. Myoepithelioma is defined as “a benign salivary gland tumor composed almost exclusively of sheets, islands or cords of cells with myoepithelial differentiation that may exhibit spindle, plasmacytoid, epithelioid or clear cytoplasmic features” (1). While myoepithelioma can be accepted as a separate and distinct entity (1,2), this tumor may represent one end of the histologic spectrum of pleomorphic adenoma (3–7).

Clinical features. The incidence of myoepithelioma is 1.5% of all salivary gland neoplasms and it accounts for 2.2% and 5.7% of all benign major and minor salivary gland tumors, respectively (2). However, myoepithelioma is probably not as rare as has been previously suggested. The age of patients ranges from 9 to 85 years, with an average of 44 years, but there is no significant gender predilection (1). Myoepithelioma occurs most frequently in the parotid gland (40%), followed by the palate (21%) and submandibular gland (10%) (1). Other minor salivary and seromucinous gland sites can also be affected. The skin, lung, and soft tissue have rarely been reported as the primary site of myoepithelioma (8–10). It presents as a slow-growing, painless mass, which is clinically indistinguishable from pleomorphic adenoma. Rarely, myoepithelial carcinoma arises from a preexisting myoepithelioma (11).

Pathology. Grossly, myoepithelioma presents as a well-circumscribed solid mass with a white to tan colored cut surface (Fig. 52). The size of the tumor ranges from 1 to 5 cm in diameter, but is usually less than 3 cm.

Microscopically, the tumor is surrounded by a thin fibrous capsule in the parotid gland but is often not encapsulated when located in the minor salivary or seromucinous gland sites. As with pleomorphic adenoma, a pushing margin with pseudopodia can be seen in myoepithelioma, but the tumor does not show destructive invasive growth. It is composed of solid, sheetlike, myxoid, microcystic, or reticular growth patterns of neoplastic myoepithelial cells exhibiting variable morphologies (Fig. 53) (4). In many myoepitheliomas,

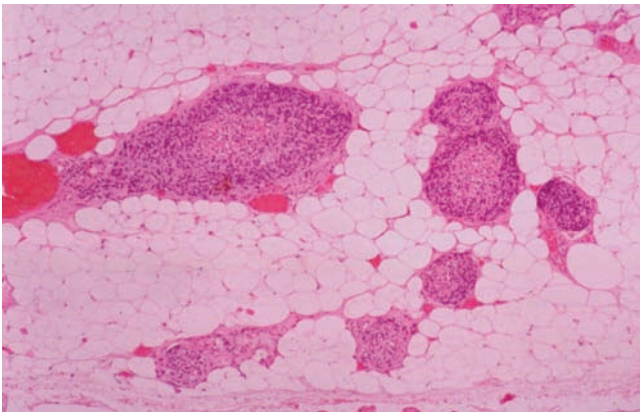


Figure 51 Multifocal recurrent pleomorphic adenoma in periparotid adipose tissue.

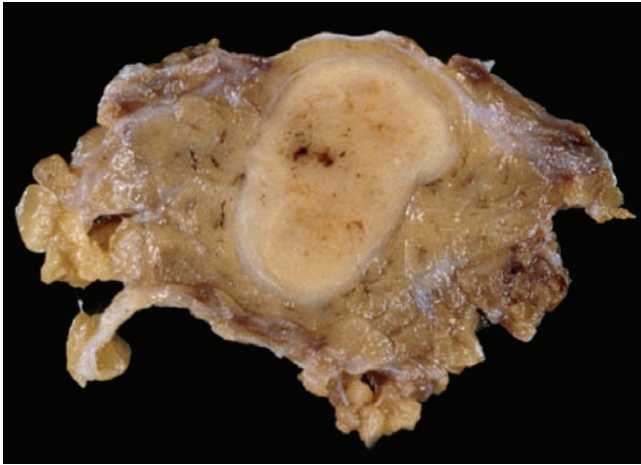


Figure 52 Myoepithelioma. The cut surface of a tumor presents as a well-circumscribed, yellow-tan colored, solid mass in the parotid gland.

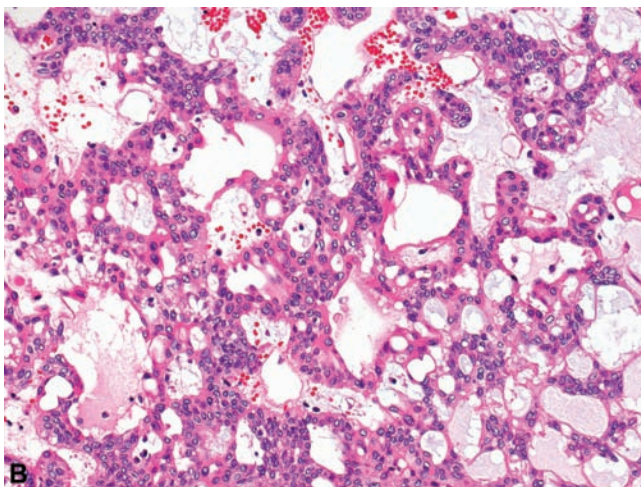
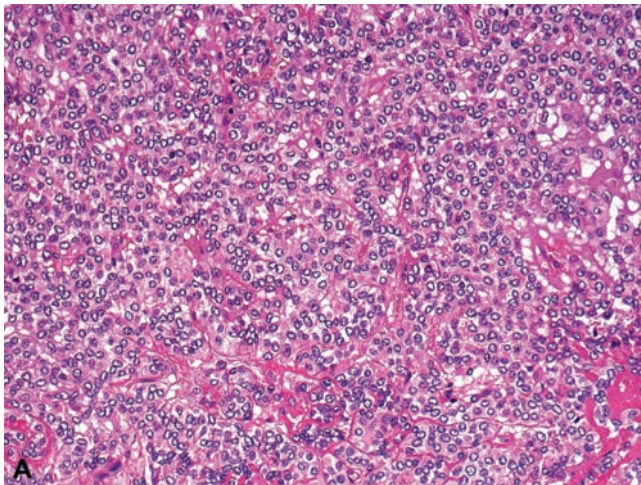


Figure 53 Myoepithelioma. Solid (A) and reticular (B) growth patterns of neoplastic myoepithelial cells.

combinations of these patterns may be present within the same tumor mass. Collagenous crystalloids in the form of radially arranged and intercellular hyaline material can occasionally be observed (12).

The neoplastic cells may be spindle, plasmacytoid, epithelioid, or clear type (Fig. 54). The spindle-cell type is the most common, but a mixture of several types of the cell within a tumor is often seen (4). Tumors with predominant spindle cells are frequently observed in the parotid gland, whereas palatal tumors consist mainly of plasmacytoid cells. The spindle cells have centrally located nuclei and are usually arranged in an interlacing fascicular pattern (Fig. 54A). A case of spindle-cell type of myoepithelioma with extensive lipomatous metaplasia has been reported (13). The plasmacytoid cells, also referred to as "hyaline cells," have eccentrically located nuclei and abundant eosinophilic cytoplasm, bearing a superficial resemblance to plasma cells, but these lack perinuclear halos (Fig. 54B) (14). In addition, the plasmacytoid cells of myoepithelioma are much larger than plasma cells. Aggregations of plasmacytoid cells are often surrounded by a myxoid matrix. The epithelioid cells are polygonal, possessing central nuclei and pale eosinophilic cytoplasm (Fig. 54C). These cells may be arranged in patternless sheets, cords, reticular configurations, or trabeculae. The clear cells are polygonal in shape and have abundant glycogen revealed by PAS stain, with or without diastase digestion (Fig. 54D). Tumors with predominant clear cells are extremely rare. Oncocytic variants of myoepithelioma have also been reported (15). Cells of intermediate appearance are sometimes present among cells of different types. Cellular pleomorphism is usually absent but may be observed to a mild degree in some tumors. Mitoses are generally scanty [up to 6 mitotic figures/10 HPFs (high-power fields)]. The stroma may be hyalinized or myxoid. Interstitial hyaline deposition is occasionally seen.

Although some investigators accept chondroid differentiation in myoepithelioma (4), we prefer that typical chondroid area of a pleomorphic adenoma should not present in myoepithelioma. Ductal differentiation is usually absent, but the presence of very rare foci of ductal structures (up to 5%), usually at the periphery of the tumor, does not preclude a diagnosis of myoepithelioma (1,4,7).

Ultrastructural studies indicate both the epithelial and smooth muscle nature of the tumor cells in myoepithelioma (4). The tumor cells contain microfilaments, usually without focal densities in their cytoplasm and have desmosome-like junctions (Fig. 55).

Immunohistochemistry. Myoepitheliomas are consistently immunoreactive for pan-cytokeratin (Fig. 56A), S-100 protein (Fig. 56B), vimentin, and p63 (16–19). Positivity for calponin (Fig. 56C), smooth muscle actin, cytokeratin 14, caldesmon, muscle-specific actin, glial fibrillary acidic protein, and smooth muscle myosin-heavy chain vary according to the case or cell type (16–19). Generally, smooth muscle actin is often expressed in spindle cells but not in plasmacytoid cells (12). Calponin is considered the most specific and generally sensitive marker for neoplastic myoepithelial cells (19). Epithelial membrane antigen

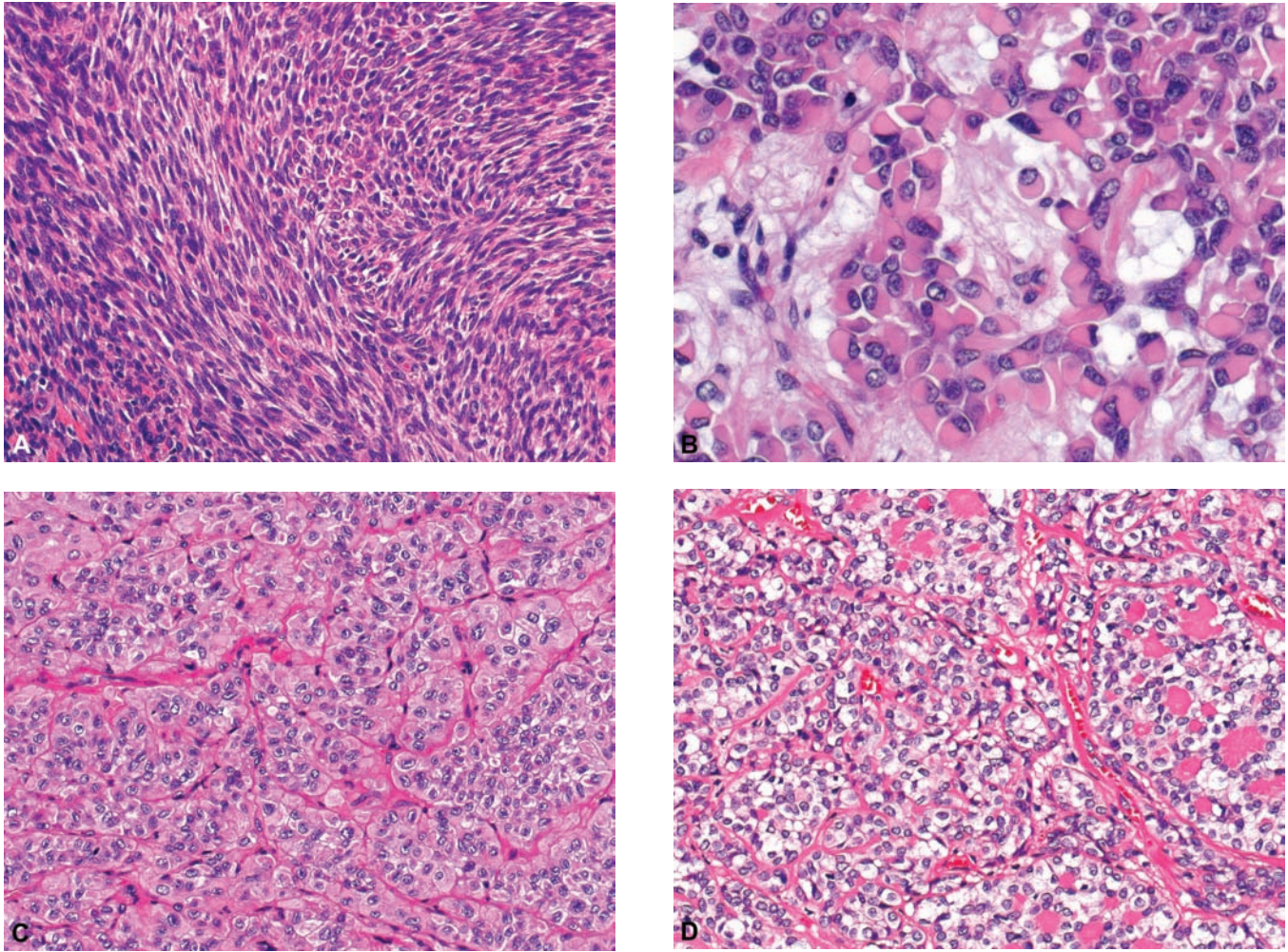


Figure 54 Myoepithelioma. (A) Spindle cell type. The spindle cells are arranged in an interlacing fascicular pattern. (B) Plasmacytoid cell type. The plasmacytoid cells exhibiting eccentrically located nuclei and abundant eosinophilic cytoplasm are surrounded by a myxoid matrix. Note the lack of perinuclear halos seen in the true plasma cells. (C) Epithelioid cell type. Solid and trabecular growth patterns of polygonal epithelial cells with central nuclei, and eosinophilic cytoplasm. (D) Clear cell type. Solid growth of polygonally shaped clear cells with intercellular hyaline depositions.

is usually negative. Positive immunoreactivity for pan-cytokeratin in conjunction with one or more myoepithelial markers may be required for the diagnosis of myoepithelioma.

Differential diagnosis. Since neoplastic myoepithelial cells exhibit considerable morphogenic heterogeneity, myoepithelioma must be distinguished from various other tumor types. Spindle cell mesenchymal tumors, such as extracranial meningioma, schwannoma, leiomyoma, benign fibrous histiocytoma, and synovial sarcoma, should be considered in the differential diagnosis of spindle cell variant of myoepithelioma.

The plasmacytoid variant must not be misdiagnosed as plasmacytoma. Immunohistochemical examination for cytokeratin and specific myoepithelial markers, including calponin and smooth muscle actin, is useful in distinguishing between myoepithelioma

and spindle cell mesenchymal tumors or plasmacytoma. In addition, myoepithelioma should be differentiated from its malignant counterpart, myoepithelial carcinoma. In most instances, these two neoplasms can easily be distinguished by histologic hallmarks such as invasiveness, cellular pleomorphism, necrosis, and frequency of mitosis. Immunohistochemical assessment of the Ki-67 labeling index is helpful in the differential diagnosis between myoepithelioma (range: 0.9–9.1%, mean: 5.4%) and myoepithelial carcinoma (range: 15.6–65.3%, mean: 35.0%) (11).

Treatment and prognosis. The treatment and prognosis of myoepithelioma are essentially the same as those of pleomorphic adenoma, because both tumors have a similar biologic behavior. Complete surgical excision is the treatment of choice for myoepithelioma. Recurrence after appropriate treatment is unusual and the prognosis is excellent. Rarely,

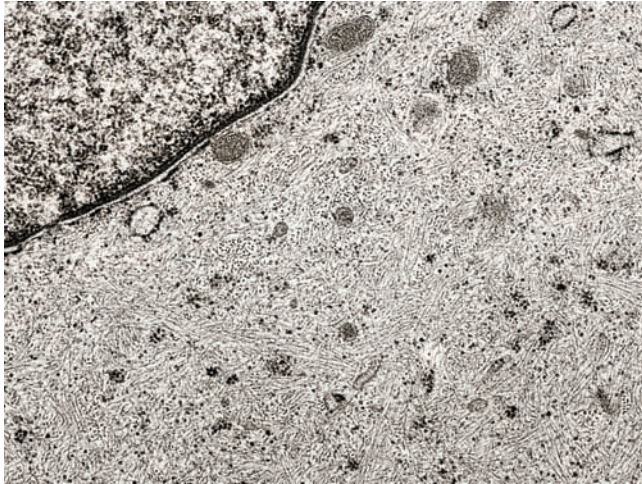


Figure 55 Myoepithelioma. Electron microscopy of the tumor cell reveals abundant microfilaments without focal densities in the cytoplasm.

long-standing or recurrent myoepitheliomas undergo malignant transformation (20).

Basal Cell Adenoma

Introduction. In normal salivary glands, basal cells are localized to ducts and have a relatively isomorphic appearance, with palisade-like, polarized nuclei (1). Unlike myoepithelial cells, basal cells do not have myofilaments and their functional role is poorly understood. Although basal cells are found in several salivary gland tumors, those composed predominantly of basal cells are relatively uncommon. In 1967, Kleinsasser and Klein first described basal cell adenoma, which was an encapsulated, slow-growing, purely epithelial neoplasm composed of what appear to be basal cells (2). Basal cell adenoma is distinctly separate from pleomorphic adenoma because of its uniform population of tumor cells, in contrast to the diverse histopathologic features commonly seen in the latter tumor. Basal cell adenoma was categorized as other types of *monomorphic adenomas* in the first edition of the *WHO Classification of Salivary Gland Tumors* (3–8). However, it was placed in a specific category in the second, and, as in the 2005 WHO classification (9,10), the term “*monomorphic adenoma*” did not appear. Formerly, some authors included canalicular adenoma as a variant of basal cell adenoma (11), but now it is regarded as a separate entity because of its characteristic clinical and histopathologic features (9–13).

Clinical features. Basal cell adenoma is an uncommon benign tumor with the reported incidence varying from 1.0% to 7.5% of all salivary gland tumors (11,14). It occurs mainly in the major salivary glands, especially the parotid gland (8), and only a few examples have been described in the minor salivary glands, the upper lip being the most common site.

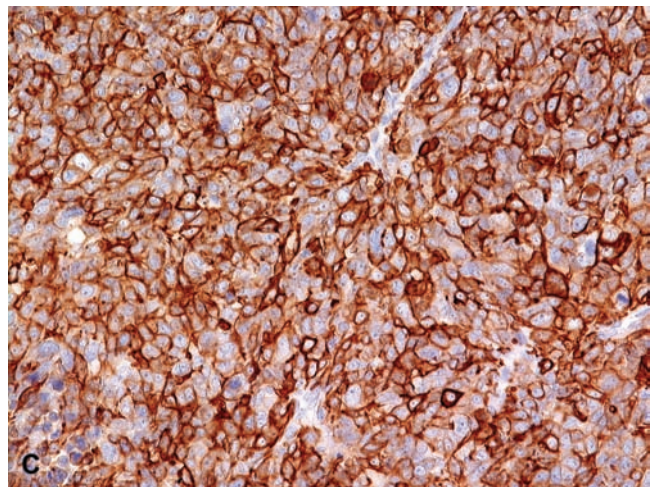
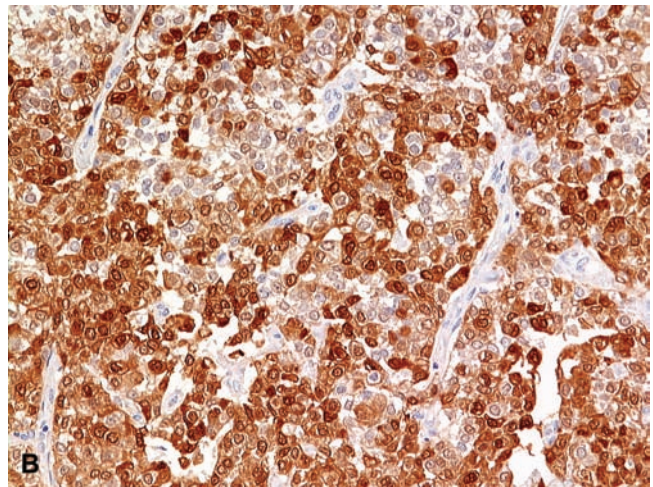
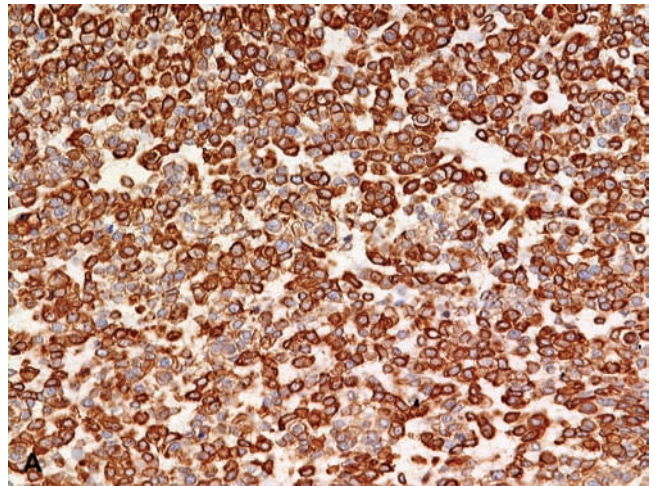


Figure 56 Myoepithelioma. Immunohistochemically, tumor cells are diffusely positive for pan-cytokeratin (A) S-100 protein (B) and calponin (C).

Basal cell adenomas develop most frequently in patients older than 50 years, and the average is 58 years, being 10 years higher than for pleomorphic

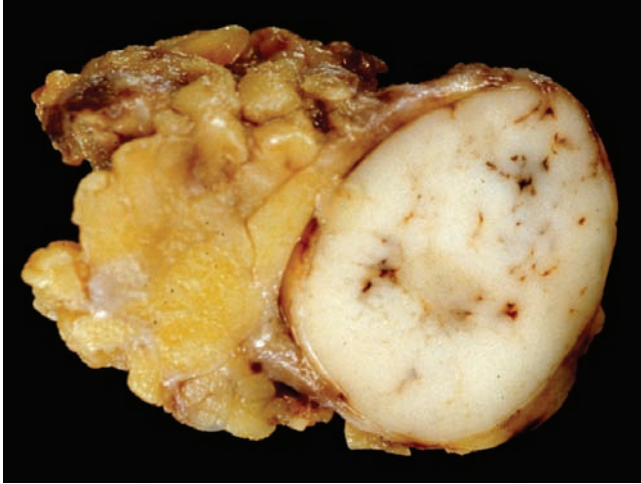


Figure 57 Basal cell adenoma. Cut surface of the parotid gland tumor shows well-circumscribed, grayish-white, solid mass.

adenoma (14). Although rare examples of congenital basal cell adenoma have been described, these tumors are best classified as sialoblastoma rather than as a special form of basal cell adenoma (11,15). There is a 2:1 female predominance for most subtypes of basal cell adenomas, although the membranous variant has no gender predilection (11). Clinically, typical basal cell adenomas present as a solitary and freely mobile, superficial parotid tumor indistinguishable from pleomorphic adenomas. However, they tend to be smaller than pleomorphic adenomas, usually not exceeding 3 cm in diameter (14).

Pathology. Basal cell adenoma is a well-circumscribed round or ovoid tumor with a distinct fibrous capsule, except for the membranous type, which has a multifocal or multinodular growth pattern. The cut surface is typically uniform and solid and varies from grayish-white to brown (Fig. 57). Their appearance has been described as similar to that of an enlarged lymph node. Formation of cysts filled with brown, mucinous material is not uncommon, though its histogenesis has not yet been elucidated. Basal cell adenomas tend to be under 3 cm in diameter with a range of 1.2 to 8 cm.

Microscopically, basal cell adenoma is composed of basaloid cells that form solid sheets, nests, cords, and ducts within a fibrous stroma (Fig. 58). Basal cell adenomas are histologically subclassified into solid, trabecular, tubular, and membranous (dermal analogue) types, according to their cellular growth pattern (Fig. 59). Although the most common type of basal cell adenoma is the solid variant, a mixture of several architectural growth patterns is commonly seen. Despite these different growth patterns, there are basic underlying histologic features that facilitate the diagnosis. The peripherally located cells in the basaloid cell nests frequently show a palisading arrangement and each nest is sharply demarcated from the stroma by basement membrane-like material.

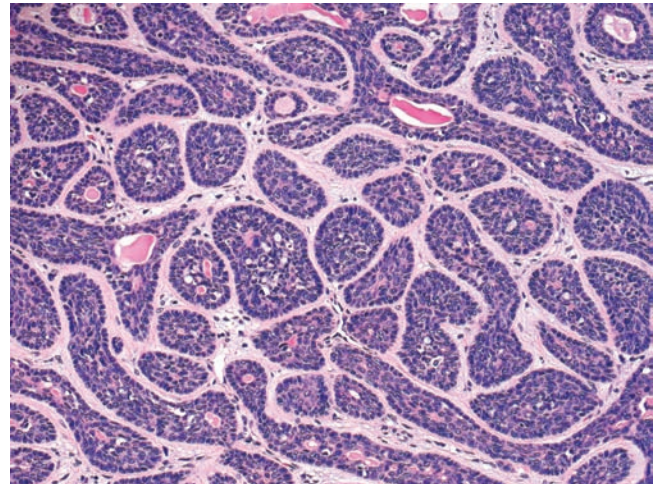


Figure 58 Basal cell adenoma. Typical feature of the tumor composed of basaloid cells forming solid islands, cords, and ducts within a fibrous stroma. Note that each nest is sharply demarcated from the stroma by basement membrane-like material, and the myxochondroid stroma characteristically observed in pleomorphic adenoma, is absent.

Importantly, the myxochondroid stroma characteristically observed in pleomorphic adenoma is absent in basal cell adenoma. Scattered tubular structures are seen within the cell nests with occasional squamous eddies. The tumor cells have two basic cell types; one has scant cytoplasm and a round, basophilic nucleus with indistinct nucleoli, and the other has a larger, paler nucleus and more abundant cytoplasm. The former cells tend to be located at the peripheral portion of the nests, whereas the latter form tubular structures. The tumor cells are isomorphic without nuclear pleomorphism. Mitotic figures and apoptotic cells may be encountered but are scanty.

The solid variant of basal cell adenoma is characterized by large sheets, broad bands, and islands of basaloid cells with peripheral palisading (Fig. 59A). Whorling patterns or squamous eddies and occasional keratin pearl formation may be observed within the cell nests. Only a few ductal structures are seen in this variant of basal cell adenoma. Cystic change is common. An adenoid cystic pattern with multiple, pseudocystic formations may sometimes be observed in basal cell adenoma, in which dilated lumina usually contain Alcian blue–positive material (Fig. 60) (14,16). The stroma is usually loose and scanty.

In the trabecular variant, cellular features are the same as those seen in the solid variant, but the epithelial islands are narrower and form an interconnecting cordlike architecture (Fig. 59B). Rarely, a richly cellular stroma composed of S-100 protein–positive, modified myoepithelial cells is seen between tumor cords (17).

The tubular variant has prominent duct-like structures with luminal cuboidal cells surrounded by one or more layers of basaloid cells (Fig. 59C).

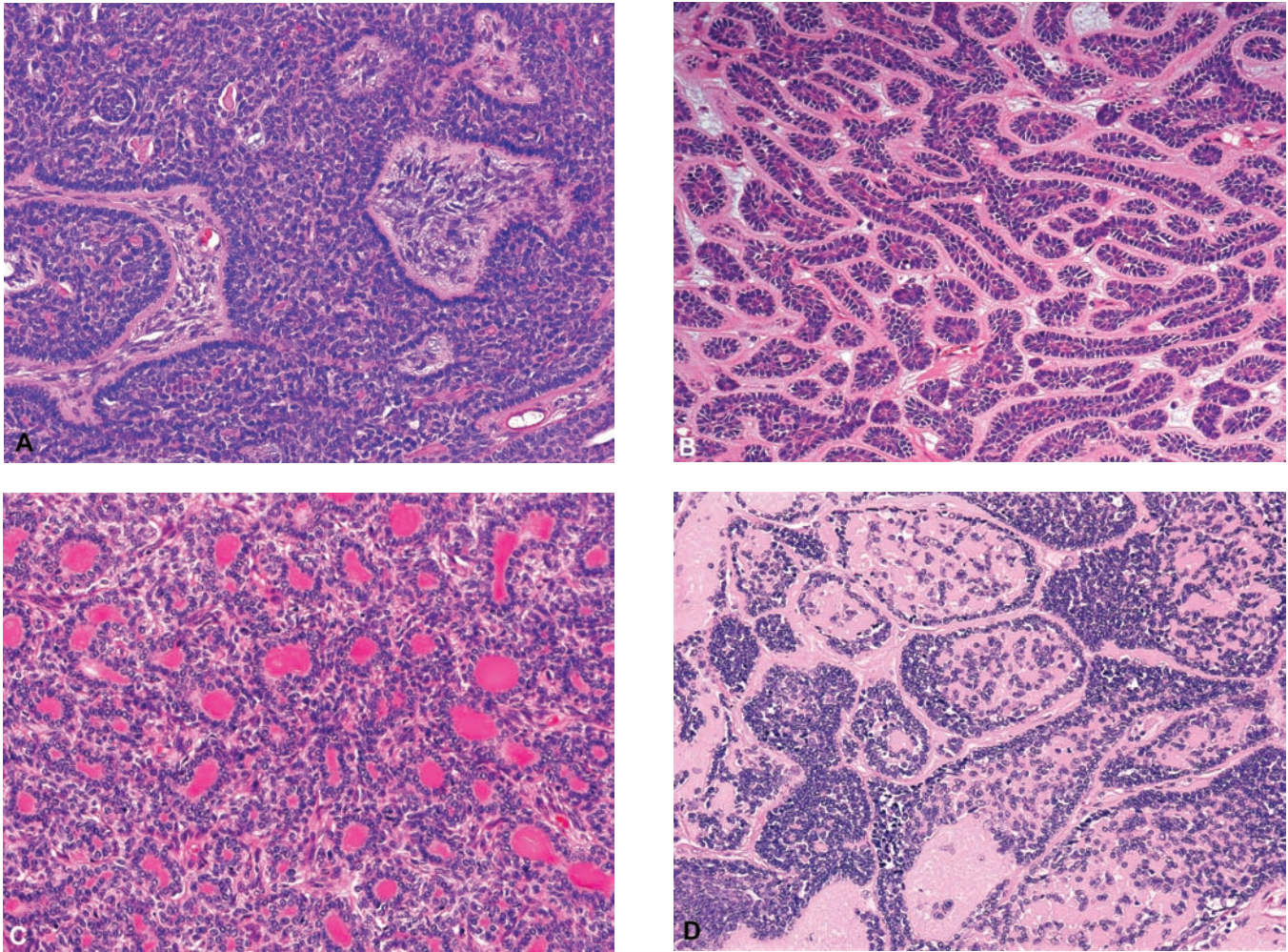


Figure 59 Basal cell adenoma. (A) Solid type. Large sheets and broad bands of basaloid cells with peripheral palisading. (B) Trabecular type. Narrow epithelial islands forming an interconnecting cordlike architecture. (C) Tubular type. Prominent duct-like structures with intraluminal eosinophilic secretion. (D) Membranous type. Thick, hyaline, basement membrane-like material surrounds large lobules. This material is also present within the epithelial nests forming coalescing, hyaline droplets.

Eosinophilic secretion is present within the ductal lumina. Since a tubular pattern may often be seen in conjunction with the trabecular pattern, some authors merge the tubular and trabecular variants into a tubulotrabecular variant. Occasionally, focal or extensive oncocytic change may be observed.

The membranous (dermal analogue) variant histologically resembles eccrine dermal cylindroma (Fig. 59D). Although the growth pattern and cellular features are similar to those of the solid variant, membranous basal cell adenoma is usually multinodular and is often not encapsulated. This multinodular growth pattern should not be misinterpreted as malignancy. The tumor cell nests tend to be arranged in large lobules surrounded by thick, PAS-positive, hyaline, basement membrane-like material, forming "jigsaw puzzle"-like patterns. This material is also present within the epithelial nests forming coalescing, hyaline droplets.

Electron microscopy. Ultrastructural observations have confirmed both ductal and myoepithelial differentiation of the tumor cells (11,18). Luminal cells exhibit microvilli, tight junctional complexes, and occasional secretory granules characteristic of ductal differentiation. Abluminal cells include centrally placed squamous cells, intermediate cells, and peripheral myoepithelial-type cells. In the membranous variant, abundant stroma and intercellularly reduplicated, multilayered basal lamina are evident.

Immunohistochemistry. Basal cell adenomas show both ductal and myoepithelial differentiation of variable degrees (19–21). Cytokeratin is detected in luminal as well as abluminal cells in all tumors. Epithelial membrane antigen is also expressed in nearly all tumors, but its distribution is confined to the apical portions of the luminal cells. The luminal aspect of cell borders and the intraluminal secretion show positive reaction for carcinoembryonic antigen.

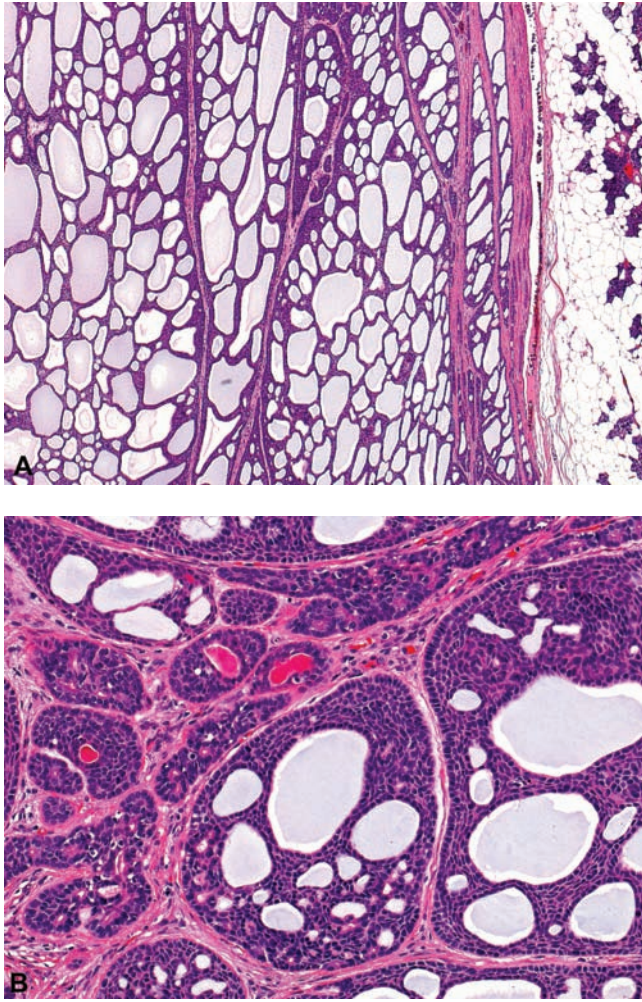


Figure 60 Basal cell adenoma with a prominent adenoid cystic pattern. (A) Well-circumscribed tumor is composed of large sheets with multiple pseudocysts forming adenoid cystic type cribriform pattern, which imparts a “Swiss cheese”-like appearance. Pseudolumina contain slightly basophilic material. (B) The peripherally located cells in the basaloid cell nests frequently show a palisading arrangement. A few true glandular lumina, some of which contain eosinophilic secretion and pseudocysts in the solid and trabecular nests.

Conversely, smooth muscle actin, calponin, p63, S-100 protein, and vimentin, indicators of myoepithelial cell differentiation may be positive and tend to localize at the periphery of the nests, adjacent to the connective tissue. Rarely, S-100 protein is strongly expressed in spindle-shaped “stromal” cells (17).

Differential diagnosis. The main differential diagnoses of basal cell adenoma include basal cell adenocarcinoma, adenoid cystic carcinoma, pleomorphic adenoma, and canaliculic adenoma (also see the section “Basal Cell Adenocarcinoma”) (1).

Basal cell adenomas and basal cell adenocarcinomas share common clinical and histologic similarities. Both tumors predominantly occur in the major

salivary glands, and four histopathologic growth patterns have been described for each lesion. Moreover, they are characterized by similar proliferation of two morphologic variants of basaloid cells. The most important diagnostic feature for separating basal cell adenomas from basal cell adenocarcinomas is the absence of infiltrative growth pattern. However, since cellular pleomorphism of basal cell adenocarcinomas is usually slight, differential diagnosis between the two is difficult in limited biopsy material. Immunohistochemical markers, demonstrating ductal epithelial and myoepithelial differentiation, display a striking similarity in basal cell adenomas and basal cell adenocarcinomas, so that they are of little value in the differential diagnosis. However, a higher rate of cell proliferation (>4 mitotic figures/10 HPFs or over 5% of Ki-67 labeling index) and apoptosis ($>0.4\%$ of apoptotic index determined by terminal deoxynucleotidyl transferase-mediated dUTP-digoxigenin nick end labeling method), along with strong expression of p53 and epithelial growth factor receptor, and loss of bcl-2 expression may be diagnostic for basal cell adenocarcinomas rather than basal cell adenomas (21).

Because cribriform structures may sometimes be observed in basal cell adenomas, it is necessary to distinguish it from adenoid cystic carcinoma (14). These appearances can be differentiated from adenoid cystic carcinoma on the basis of the gradual structural alteration from areas typical of basal cell adenoma. In addition, other features characteristic of adenoid cystic carcinoma, such as cells with irregular, angular-shaped hyperchromatic nuclei, mitoses, or invasive growth are absent in the adenoid cystic carcinoma-like areas of basal cell adenoma. Furthermore, the peripheral palisading arrangement and focal squamous differentiation with whorling pattern present in basal cell adenoma are not usually encountered in adenoid cystic carcinoma.

Although basal cells are one of the components of pleomorphic adenoma, myxochondroid stroma and the plasmacytoid cells characteristically observed in pleomorphic adenoma are absent in basal cell adenoma. Canaliculic adenomas can be distinguished by their double row of low columnar cells arranged in parallel branching cords. In addition, canaliculic adenoma shows exclusively duct luminal differentiation by immunohistochemistry, whereas dual ductal and myoepithelial differentiation can be seen in basal cell adenoma (22).

Treatment and prognosis. Basal cell adenoma usually behaves in a benign fashion, analogous to that of pleomorphic adenoma, and recurrence is rare. However, the membranous form of basal cell adenoma, also known as dermal anlage tumor, is associated with a higher recurrence rate (25–37%) after surgical removal (8,23). It has particular clinical associations with tumor diathesis and its histology. There have been cases of membranous basal cell adenomas in the parotid gland coexisting with multiple dermal cylindromas (turban tumors), trichoepitheliomas, eccrine spiradenomas, trichilemmomas, or basal cell carcinomas in the same patients (23–26). Furthermore, the same cytogenetic abnormality in

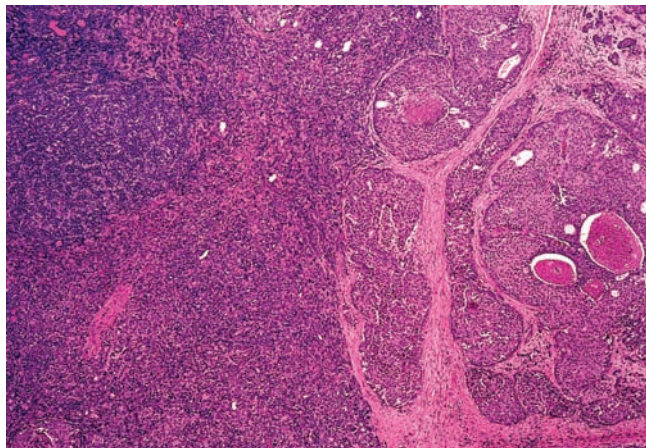


Figure 61 Carcinoma arising in basal cell adenoma. Salivary duct carcinoma composed of solid tumor nests with comedonecrosis (*right*) develops from basal cell adenoma (*left*) through the transitional zone seen in the middle.

the chromosome 16q12–13, the *CYLD* between dermal cylindromas and membranous basal cell adenomas has been reported in two familial cases (23). However, the majority of the parotid membranous basal cell adenomas occur independently of such associations. Nevertheless, it has been suggested that individuals with salivary basal cell adenomas should be screened for skin lesions. Malignant transformation of basal cell adenoma is an exceedingly rare event (8,27–30). It is reported, however, that the incidence of basaloid carcinoma arising from basal cell adenoma is higher in the membranous type with the salivary-dermal tumor diathesis (8,28). A few examples of nonbasaloid tumors, including salivary duct carcinoma and adenocarcinoma (NOS), arising in basal cell adenoma have been described (Fig. 61) (29).

Warthin's Tumor

Introduction. Warthin's tumor was first described comprehensively by the American pathologist Aldred Scott Warthin in 1929. Over the years, this tumor has been known by over 20 different names, including adenolymphoma, cystadenolymphoma, and papillary cystadenoma lymphomatosum. "Warthin's tumor" is the preferred term as this avoids possible confusion with lymphoid malignancy, and with the separate entity, lymphadenoma (1). It is defined as "a tumor composed of glandular and often cystic structures, sometimes with a papillary cystic arrangement, lined by characteristic bilayered epithelium, comprising inner columnar eosinophilic or oncocytic cells surrounded by smaller basal cells. The stroma contains a variable amount of lymphoid tissue with germinal centers" (2).

Clinical features. Warthin's tumor is the second commonest neoplasm of the salivary glands in most large series. It comprised about 3.5% of all primary

epithelial tumors in the United States and 5.3% of parotid tumors (3). Higher percentages in the parotid gland have been reported in the United Kingdom (14.4%) (4), Denmark (27.5%) (5), and Pennsylvania (30%) (6). There appears to be a much lower incidence of Warthin's tumor in ethnic groups with dark skin, including Asian populations (7), black Africans (8), and African-Americans (3), although the incidence appears to be increasing in the latter group (9). The mean age at diagnosis is 62 years, (range 2.5–92) (3), and tumors are rarely seen in the first three decades of life. There has been a striking change in the relative sex incidence over the last 50 years (10). In 1953 the male to female ratio was 10:1 (10), whereas in 1996 it was 1.2:1 (3), and in 1992 it was equal (6). This change in sex incidence coincides with an increased prevalence of smoking in women. Familial cases are rare and may be due to coincidence (11,12).

Warthin's tumor is almost exclusively limited to the parotid glands and the periparotid lymph nodes (13). Most cases involve the lower pole, although 10% are in the deep lobe. Very rare examples have been reported in other glands (14), but many tumors thought to arise within the submandibular gland have usually developed within the anterior tail of the parotid or from adjacent lymph nodes (3). Unusual locations for the tumor include the mouth (15), nasopharynx (16), larynx (15), and lacrimal gland (17). However, it is important to exclude oncocytic metaplasia of ductal epithelium of the minor glands with associated reactive lymphocytic infiltration. Warthin's tumor is the most common salivary neoplasm showing multifocality (12–20%, either synchronous or metachronous) or bilaterality (5–14%) (18,19). However, the incidence of multifocal Warthin's tumors rose to 50% when parotid glands were serially sectioned (20).

Most patients present with a slow-growing, soft mass, usually 2 to 4 cm in size; large tumors are exceptional (21). The mean duration of symptoms is 21 months, but in 41% of patients it is less than six months (10). There may be fluctuations in the size of the tumor, especially when eating (22). Pain or discomfort is relatively uncommon (9–18% of cases) (10,24) and is usually seen in the infarcted (metaplastic) variant (23). Occasionally pain may be severe and cause otalgia. Facial nerve palsy is rare, and again, is usually due to inflammation and fibrosis in infarcted tumors (24–26).

Imaging. Warthin's tumors are able to concentrate 99m Tc pertechnetate and appear as hot spots. However, scintigraphy has been found to be less useful than conventional MRI in the evaluation of Warthin's tumors (27). The tumor is usually well circumscribed, but secondary inflammation can cause blurring of the edges.

Etiology. There is a strong link between Warthin's tumor and cigarette smoking (28,29)—the incidence is eight times that of nonsmokers (30). There appears to be a higher risk of bilateral Warthin's tumor in heavy cigarette smokers (31). In addition, the increased numbers of female smokers during the second half of the 20th century closely parallels the

increase in Warthin's tumor in women and largely explains the change in sex incidence during this period (8,32). The mechanisms are not clear, but it has been speculated that irritants in tobacco smoke cause metaplasia in the parotid (33). However, Warthin's tumor develops in only a small proportion of smokers (including black Africans and African-Americans), and therefore, smoking is likely to be a promoting factor rather than the main etiologic agent (33).

Radiation exposure may be relevant as there is an increase in Warthin's tumor among atomic bomb survivors (34). There appears to be an association between Warthin's tumor and organ-specific autoimmune disease, especially insulin-dependent diabetes mellitus, Hashimoto's thyroiditis, autoimmune hyperthyroidism, and hypothyroidism (35).

The possible role of EBV in the pathogenesis of Warthin's tumor is unclear. In some cases, especially where there are multiple tumors, the EBV genome has been isolated from the cytoplasm of the luminal cells (36), but not in other studies (37). Also, EBV exposure during childhood or adolescence is widespread (38), and thus any possible etiologic role has not yet been established. At present, the balance of probabilities is that EBV does not play a significant role in the etiology of Warthin's tumor (39).

The infarcted (metaplastic) variant can follow trauma, particularly from fine-needle aspiration biopsy (39–44).

Pathology. Grossly, most Warthin's tumors are encapsulated, spheroidal to ovoid masses with a smooth and sometimes bosselated surface. Despite the circumscription, the capsule is often thin, may be incomplete, and is easily ruptured during surgical removal. The size ranges from 1 to 10 cm (mean 3.5 cm) in greatest diameter (10). Sectioning typically shows papillary cystic spaces of variable sizes that contain mucoid, clear or brown, glary fluid. In some cases, papillary infoldings are inconspicuous grossly and the tumor appears either as a unilocular cyst or as a more solid mass. The solid areas are tan to white, and may be firm and fibrous in inflamed tumors.

The microscopic appearance of a typical Warthin's tumor is very characteristic and readily recognisable. It is sharply demarcated with a thin capsule. There are cystic and solid areas, and both epithelial and lymphoid components (Fig. 62). The cysts vary considerably in size and shape, and papillary structures project into the lumina. The papillae have fibrovascular cores, often with lymphoid stroma. The epithelium is double layered with tall, columnar, luminal cells that are granular and oncocytic. There is palisading of their bland, single, ovoid nuclei located centrally or toward the luminal end of the cell (Fig. 63). The surface often shows apocrine blebbing, and cilia, as first described by Warthin, are occasionally identified (Fig. 64) (10). The abluminal layer consists of less numerous, smaller, flattened, or cuboidal basal cells. Their cytoplasm is similar to luminal cells but less abundant. No significant nuclear atypia or mitotic activity is identified. Occasionally, the luminal cells are intensely oncocytic with pyknotic nuclei (dark cells; pyknocytes) and

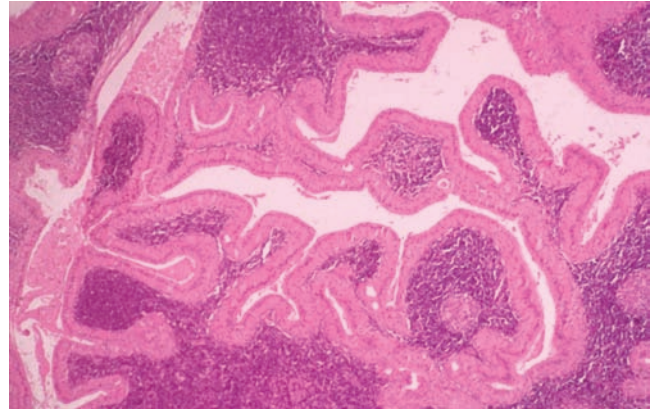


Figure 62 Warthin's tumor showing papillary cystic tumor with dense lymphoid stroma.

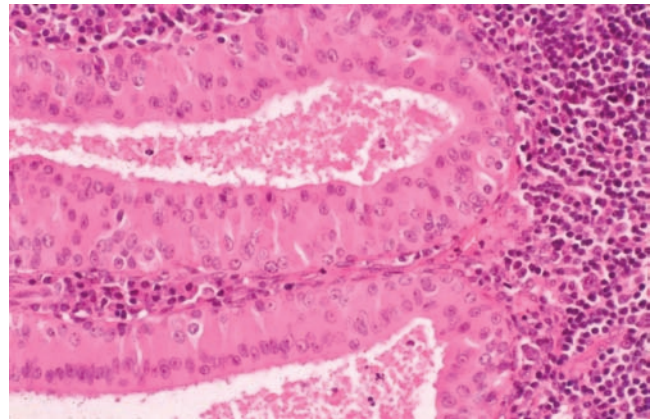


Figure 63 Warthin's tumor showing oncocytic palisaded luminal cells and less numerous and regular abluminal basal cells.

some appear to be extruding into the luminal space (Fig. 65). Small foci of squamous and mucous metaplasia are relatively common (Fig. 66), and very occasionally sebaceous differentiation is seen (45). The cystic spaces may contain eosinophilic secretions with occasional cholesterol cleft formation and rarely laminated structures resembling corpora amylacea.

The stroma consists of lymphoid tissue with varying degrees of reactivity, and germinal centers are present in the majority. Mast cells, histiocytes, and plasma cells may also be seen. The ratio of epithelium to lymphoid stroma varies between different tumors, and Warthin's tumors have been subclassified into typical (both components approximately equal), stroma-poor (epithelial component >70%) and stroma-rich forms (epithelial component of <30%) (46). However, this subdivision has no prognostic value.

Microscopic foci of inflammation, necrosis, and fibrosis are common, and minor degrees of squamous

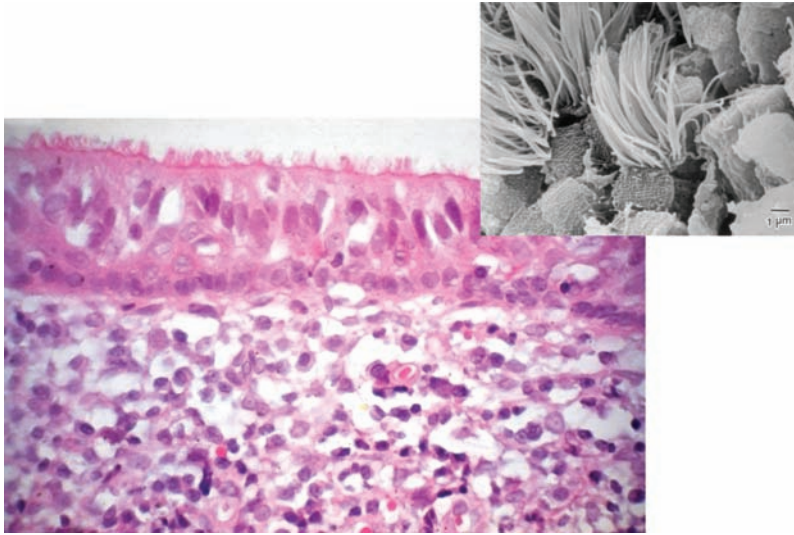


Figure 64 Warthin's tumor with ciliated epithelium. Inset: Scanning electron micrograph. *Source:* Courtesy of Professor Hwang.

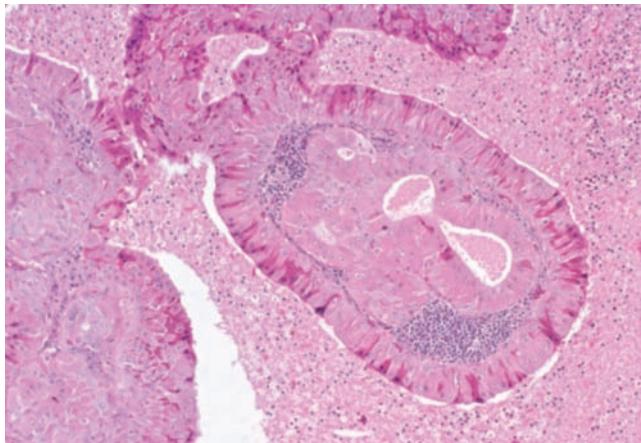


Figure 65 Warthin's tumor with epithelium showing light and dark (pyknocytes) cells.

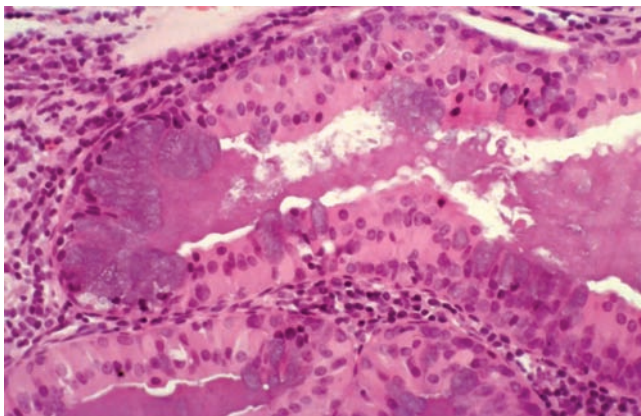


Figure 66 Warthin's tumor showing mucous metaplasia.

and mucous metaplasia were reported in 51% and 27%, respectively, of typical Warthin's tumors (39). However, in some cases there is almost complete replacement of the lymphoid and, occasionally, the epithelial component by fibrous and inflammatory tissue. This subtype has been variously termed "infarcted," "infected," or "metaplastic," and it accounts for 6% to 7% of Warthin's tumors (24,46). Although such necrosis may be spontaneous, it is likely that this variant will be seen more frequently with the increasing use of preoperative fine-needle aspiration. There is extensive necrosis but in some cases the ghost outlines of papillary structures may be seen and highlighted by a reticulin or keratin stain. There may be conspicuous squamous metaplasia, which can produce a pseudoepitheliomatous appearance. Such florid squamous change was a common feature of the "metaplastic" variant of Warthin's tumor described by Seifert et al. (46). However, 40% of these cases had received radiotherapy, a form of treatment virtually never used for these tumors currently. Focal areas of mucous metaplasia or solitary mucocytes can be present. Cytologic atypia can be prominent, and although mitotic figures may be numerous, they are normal. There is often extensive fibrosis, particularly at the periphery of the tumor, with dense collagen and myofibroblastic proliferation. There is a heavy mixed inflammatory infiltrate, often with sheets of macrophages, some with foamy cytoplasm. Lipogranulomas, cholesterol clefts, and hemosiderin deposition may be present. Epithelioid granulomas, with or without multinucleated giant cells (47), can lead to confusion with sarcoidosis and tuberculosis (Fig. 67). This differential diagnosis can be difficult, as cases of *Mycobacterium tuberculosis* infection have been reported in Warthin's tumor and confirmed by polymerase chain reaction (48). In some infarcted tumors, areas of residual Warthin's tumor may be absent, and the diagnosis then becomes implicit (24,40).

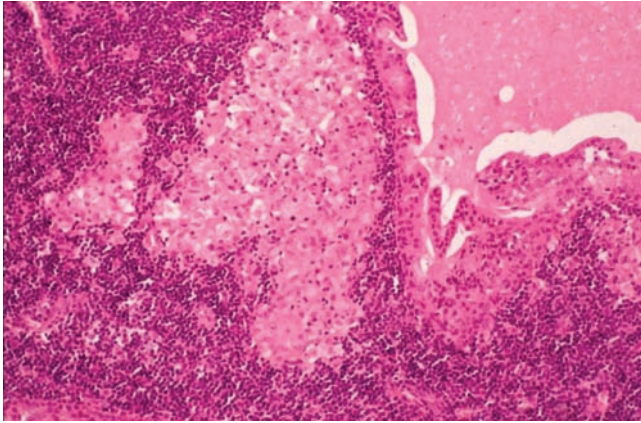


Figure 67 Warthin's tumor. An area close to infarcted tumor showing epithelioid granuloma formation.

There are two principal theories of the histogenesis (3): The more favored is an origin from intercalated and basal cells of heterotopic salivary ductal inclusions in intra- or periparotid lymph nodes. In particular, this explains the distribution of Warthin's tumor and its absence from other salivary tissue lacking incorporated lymph nodes. It has been suggested that Warthin's tumor initially develops in a parotid lymph node as an adenomatous epithelial proliferation responding to as yet unidentified stimuli (probably including tobacco, either as a direct stimulus or a promoter). This attracts a heavy lymphoid reaction, similar to that seen in certain other salivary neoplasms (49–51). The stage of this process seen at the time of surgery determines the proportions of epithelial and lymphoid elements (52).

Analysis of the X chromosome-linked HUMARA showed that Warthin's tumor is nonclonal, and thus likely to be nonneoplastic (53). It has therefore been suggested that Warthin's tumor should be classified in the group of tumorlike lesions rather than adenomas (54). This finding supports morphologic observations that have suggested Warthin's tumor (as well as various thymic and head and neck cysts) results from the induction of cystic changes in branchial cleft epithelium by an inflammatory infiltrate, accompanied by oncocyctic change in the epithelium (55).

Immunohistochemistry. All epithelial cells stain with broad spectrum cytokeratin antisera such as AE1/AE3 and MNF116, and the luminal cells are positive for cytokeratins 7, 8, and 18. Results with other cytokeratin markers are inconsistent; one study found cytokeratins 5/14 and 17 largely restricted to the basal cells, except in the metaplastic variant when they were also expressed by regenerative surface cells (56). However, other investigators have found more widespread reactivity for cytokeratin 14 in the typical type, including the surface cells (57). Cytokeratins 10/13, 1/2/11/12, and 20 were all negative, although a more recent study identified cytokeratin 10 staining in four of six tumors (58). Both layers

are positive with antimitochondrial antibodies (57), and the inner cells express epithelial membrane antigen (59). Amylase, vimentin, S-100 protein, and myoepithelial markers are negative in both basal and luminal cells. The MIB1 index is low in the usual forms, but high in regenerative squamous epithelium in the metaplastic variant.

Lymphoid marker studies have shown B (CD20), NK (CD56), and T (CD3) cells, including helper (CD4) and suppressor (CD8) subtypes. This profile of lymphocyte subsets is similar to that in normal or reactive lymph nodes (60).

However, in practice, special stains and immunohistochemistry have little to offer in the diagnosis of typical type of Warthin's tumor, although there may be a role in diagnosing the metaplastic variant, particularly when no residual viable Warthin's tumor can be identified in hematoxylin and eosin-stained specimens (40,58).

Electron microscopy. The luminal cells, and to a lesser extent the basal cells, contain abundant, variably sized mitochondria, ranging from normal to enlargement by threefold. Many display long cristae, which form lamellar sheaves, rouleaux, or concentric rings (61). The luminal cells have surface microvilli and sometimes cilia (Fig. 64) (22), and the basal cells have prominent tonofilament bundles and desmosomal attachments to each other and overlying luminal cells. These are particularly plentiful in the metaplastic subtype. Beneath the basal cells there is a narrow, discrete, basal lamina (62).

Molecular-genetic data. Cytogenetic studies have shown Warthin's tumor to have three main stemline groups, one with a normal karyotype, a second with numerical changes only (loss of Y chromosome or trisomy or monosomy 5), and a third group involving structural changes with one or two reciprocal translocations (22). Damage to the mitochondrial DNA may account for the ultrastructural changes seen in the mitochondria, as well as the oncocyctic change seen morphologically (63). There appears to be no evidence of DNA mismatch repair defects, and tumors do not show microsatellite instability (64). The chromosomal translocation t(11;19)(q21;p12–13) is seen in both Warthin's tumor and mucoepidermoid carcinoma (65). In addition, a novel gene of unknown function designated WAMTP1 (Warthin and Mucoepidermoid tumor Translocation Partner gene 1) has been described (66). This links with the mastermind-like Notch coordinator gene MAML2, and the fusion product has been shown to alter the Notch-signaling pathway, suggesting this may be important in the genesis of both mucoepidermoid carcinoma and Warthin's tumor.

Differential diagnosis. The typical type of Warthin's tumor is easily diagnosed. Papillary cystadenoma has a similar epithelial component but lacks the lymphoid elements. There is some resemblance to other lymphoepithelial cystic lesions such as simple benign lymphoepithelial cyst (unrelated to AIDS), LESA with cystically dilated ducts, cystic lymphoid hyperplasia of AIDS, and MALT lymphoma with cystically dilated

ducts (49). All lack the characteristic bilayered oncocytic epithelium of Warthin's tumor, and lymphoepithelial lesions (epimyoeplithelial islands) are usually found in LESA, MALT lymphoma, and cystic lymphoid hyperplasia of AIDS, but not in Warthin's tumor. An important differential is from cystic metastases in intra- and periparotid lymph nodes. The malignant nature of most should be obvious, but a recently reported variant of papillary thyroid carcinoma has been described as "Warthin-like" (67,68). It is characterized by a heavy lymphoid stroma and oncocytic metaplasia of the epithelium. The best guide to its true nature is that the nuclei display typical chromatin clearing, inclusions and groove formation, and the epithelial cells show immunohistochemical expression of thyroglobulin.

If there is marked cytologic atypia and mitotic activity, the metaplastic variant can be mistaken for squamous or mucoepidermoid carcinoma, either primary or metastatic (40). The resemblance is particularly close if there has been total infarction of the original Warthin's tumor. Also, the squamous metaplasia lacks keratinization (seen in most squamous carcinomas), and mucocytes are usually much less numerous than in low-grade cystic mucoepidermoid carcinoma.

Treatment and prognosis. In some cases, if the diagnosis can be confidently established, active treatment may not be necessary. Surgery, either superficial or limited parotidectomy, or local resection, is usually curative (69). The low reported rate of recurrence in most series (about 2–5.5%) (3,10) is probably the result of multifocal tumors.

Malignant change is seen in less than 1% of cases (46,70). It can involve the epithelial or lymphoid components and in some cases there is a history of previous radiation (34,46). Carcinomas that have been reported include squamous (71), adenocarcinoma (46), mucoepidermoid (72,73), oncocytic (74), Merkel cell (75), and undifferentiated. Lymphoproliferative disorders associated with Warthin's tumor include follicular lymphomas (76,77), Hodgkin's lymphoma (78,79) and peripheral T-cell lymphoma (80). Unique cases of a MALT-type lymphoma and Warthin's tumor presenting in the same parotid gland (81), and a small lymphocytic lymphoma forming a collision tumor, have been reported (82).

Warthin's tumor is the most common neoplasm seen in association with other salivary tumors, particularly pleomorphic adenoma (14,83–85). In addition, there may be an increased association with the development of extrasalivary neoplasms. This may be due to a common etiology of cigarette smoking in carcinomas of the lung, larynx, and possibly the bladder, but in sites such as the hematolymphoid system, kidney, and breast, the relationship could be coincidental (17).

Oncocytoma

Introduction. Oncocytoma is defined as "a benign tumor of salivary gland origin composed exclusively of large epithelial cells with characteristic

bright eosinophilic granular cytoplasm (oncocytic cells)" (1). Synonyms include oncocytic adenoma and oxyphil adenoma.

Clinical features. Oncocytoma is an uncommon tumor and accounted for about 1.4% of primary epithelial salivary gland neoplasms in an Armed Forces Institute of Pathology (AFIP) series (2). It is seen predominantly in elderly patients, with an average age of about 64 years. There is no racial or gender predilection. In one major study 20% of patients gave a history of previous radiotherapy to the head and neck or upper torso or long-term occupational exposure (3). The average age of these patients was 20 years younger than those not exposed to radiation (43 vs. 63 years) (3). The large majority of oncocytomas arise in the parotid (78%) and submandibular (9%) glands (2,4). Less commonly they occur in the minor salivary glands of the buccal mucosa, palate, lip, tongue, and elsewhere (2,5–7). They usually present as a unilateral painless swelling. Rare bilateral tumors have been reported (8–10).

Pathology. Grossly, oncocytomas in major glands form a single, well-circumscribed but often lobulated mass, which rarely exceeds 4 cm in diameter. The cut surface is uniform pink to rust-colored, and occasionally there are small cysts or central stellate scarring.

Microscopically, oncocytomas are encapsulated and are solid with a variable cystic component. They are composed predominantly of typical 'light' oncocytes with smaller numbers of dark cells (pyknocytes) (Fig. 68). These cells are arranged in sheets, nests, trabeculae, or duct-like structures separated by thin, fibrovascular stroma. Microcysts or macrocysts are occasionally seen. Focal clear cell change is common and occasionally the entire tumor consists of clear cells (Fig. 69) (11). It has been shown that the clear cell change is due to a combination of fixation artefact and intracytoplasmic glycogen accumulation (11,12). Occasionally there may be binucleated or atypical nuclear forms. Foci of sebaceous and squamous metaplasia may also be apparent (3). Areas of chronic

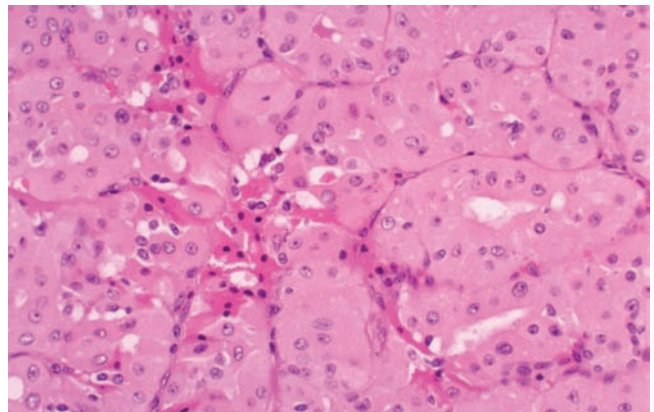


Figure 68 Oncocytoma consisting of characteristic light and dark cells.

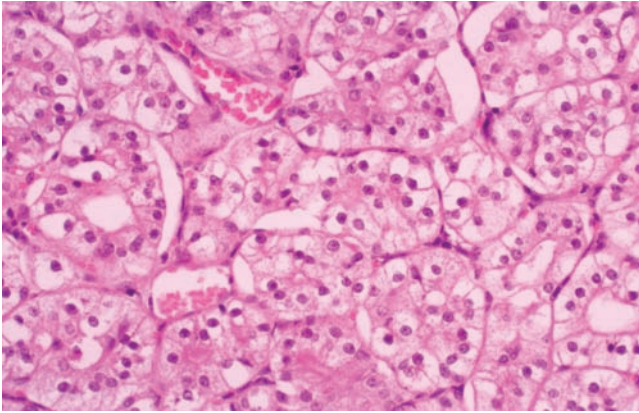


Figure 69 Oncocytoma with clear cell change.

inflammation are occasionally present. Oncocytomas may be seen in combination with multifocal nodular oncocytic hyperplasia (13).

Differential diagnosis. The differential diagnosis of oncocytoma includes other salivary gland tumors with an oncocytic component, salivary tumors consisting of large cells with granular cytoplasm, and clear cell neoplasms. Oncocytic metaplasia can be seen in a wide range of salivary gland tumors, including pleomorphic adenoma, basal cell adenoma, mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and adenocarcinoma (14–16). This metaplasia is usually focal and rarely causes diagnostic difficulties. However, occasionally in pleomorphic adenoma (17) and mucoepidermoid carcinoma (18–20) almost the entire tumor may show oncocytic change. Careful examination usually reveals more specific features of these tumors such as hyaline cells and myxochondroid matrix in pleomorphic adenoma and mucocytes in mucoepidermoid carcinoma. An “oncocytoid” artefact due to diathermy used during surgery has been described, and this can be confused with oncocytosis or oncocytoma (21). Tumors with a significant granular cell component include acinic cell carcinoma and granular cell tumor. Staining with PAS with prior diastase digestion shows that the intracytoplasmic granules of acinic cell carcinoma are positive, whereas those in oncocytomas are negative. Staining with PTAH may also aid distinction. Granular cell tumors have been rarely reported in salivary glands (22). The cells of this tumor are S-100 protein-positive, and distinction from oncocytoma should not be difficult. The differential diagnosis of clear cell salivary neoplasms is considered on page 562.

Treatment and prognosis. Although oncocytomas are benign tumors, reported rates of recurrence vary from 0% to 30% within periods ranging from 6 months to 13 years (23). Recurrences are probably due to incomplete resections or multifocal disease. Both primary and recurrent oncocytomas should be

treated by surgical excision. Oncocytes are radio-resistant and although radiotherapy has been used in the past (24), it should play no role in the management of oncocytoma.

Canalicular Adenoma

Introduction. Canalicular adenoma is defined as “a tumor composed of columnar epithelial cells arranged in thin, anastomosing cords with a beaded pattern. The stroma is characteristically paucicellular and highly vascular” (1). Synonyms include basal cell adenoma (canalicular type), monomorphic adenoma (canalicular type), and adenomatosis of minor salivary glands.

Clinical features. Canalicular adenoma is an uncommon, benign salivary tumor that arises almost exclusively in minor glands where it accounts for 4% to 6% of all tumors (2,3). It is seen predominantly in adults, with a mean age of 65 years and a range from 33 to 88 years; it is uncommon before the sixth decade (2–5). The sex ratio has varied from a definite female preponderance of 1.8:1 (2) to a slight male predominance (5) or no significant gender difference (6). The upper lip is the most common site, accounting for about 70% to 80% of cases (2,4,5). The buccal mucosa and palate are the next most common sites (3,7). It is rare in the parotid gland (3–9) and no cases have been reported in the submandibular or sublingual glands (3). Canalicular adenomas are occasionally bilateral (10,11) or multifocal, usually in the upper lip and buccal mucosa (6,12–14). Tumors typically present as slow-growing, painless masses but infarcted (15) or traumatically ulcerated tumors (4,16) may be painful. The mass is usually mobile and can be solid or fluctuant. The overlying mucosa may be normal in color, or bluish, when the tumor resembles a salivary mucocele. Canalicular adenomas rarely exceed 2 cm in diameter and the mean size is 1.7 cm (2). The duration of the tumor has varied from a few months to 15 years, with a mean of 8.4 years (2).

Pathology. Grossly, most canalicular adenomas range between 0.5 and 2 cm in maximum diameter, and they are well circumscribed and variably encapsulated. In one series nearly a quarter of tumors had multifocal nodules (5). The cut surface varies from light yellow to tan, and there are frequently cystic spaces filled with clear or lightly stained gelatinous material. Microscopy of larger tumors usually confirms the circumscribed and encapsulated nature of the neoplasm but smaller tumors and multifocal nodules frequently lack a capsule (2,12). Small foci of adenomatous change may be seen in adjacent minor glands. The most distinctive feature of canalicular adenoma is the formation of parallel rows of cuboidal or columnar cells forming a single layer (Fig. 70). The rows of cells may be closely opposed or show focal areas where they separate to form a characteristic beaded pattern. The cells are cytologically bland and have moderate amounts of eosinophilic cytoplasm and uniform, oval, or round basophilic nuclei. The latter contain diffuse, finely granular chromatin, and prominent nucleoli are uncommon. Mitoses are rarely

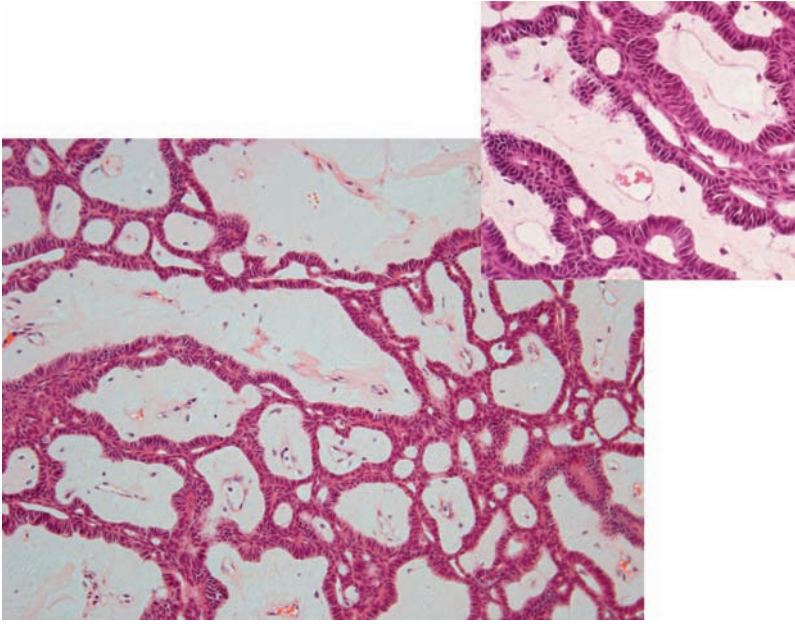


Figure 70 Canaliculal adenoma showing bilayered trabeculae of columnar cells in degenerative stroma.

seen in the absence of an inflammatory overlay (15). There may be foci of mucous, or more rarely oncocytic, metaplasia (2,16). The cellular strands are usually sharply demarcated from the surrounding stroma. This may be loosely collagenized but it is frequently sparsely cellular and myxoid, producing a microcystic appearance. In addition, the stroma may contain a conspicuous network of congested capillaries with surrounding cuffs of eosinophilic collagen (1). There may be areas of hemorrhage and associated hemosiderin deposition, together with patchy inflammatory infiltration. Extensive necrosis may follow infarction of the tumor (15). Occasionally, the solid tumor element forms no more than a mural thickening projecting into a unilocular cystic space. There may be papillary epithelial projections into the cystic spaces, and this is sometimes associated with the presence of psammoma bodies (2,16).

Immunohistochemistry. Canaliculal adenomas are positive for cytokeratins and S-100 protein and may show more variable staining for vimentin and glial fibrillary acid protein (17–20). They are negative for more sensitive markers of myoepithelial differentiation such as calponin, α smooth muscle actin, and smooth muscle myosin heavy chain (21). In addition, the tumor is negative for carcinoembryonic antigen, p53, p63, and p73 (18,22). Analysis of the cytokeratin subsets showed that most of the cells stained strongly for cytokeratins 7 and 13, but staining for cytokeratin 19 was weak (20). Cytokeratins 8 and 19 were only found in occasional cellular aggregates or scattered individual cells.

Differential diagnosis. The main differential diagnoses are basal cell adenoma and adenoid cystic carcinoma. The characteristic bilayered cellular strands and distinctive stromal degeneration of canaliculal adenoma should aid the separation from

trabecular or tubulotrabeular basal cell adenomas. In addition, the tumors have distinctive immunohistochemical profiles, particularly in regard to myoepithelial differentiation (21). However, occasional tumors show a hybrid morphology making meaningful distinction impossible (23). As both tumors behave in a similar fashion, the separation has little clinical importance. Notable features that help distinguish canaliculal adenoma from adenoid cystic carcinoma include its circumscribed nature, with no evidence of invasion, and the characteristic vascularity of the stromal component (24). In equivocal cases, or when there is evidence of multifocality, the absence of staining with myoepithelial markers may aid distinction.

Treatment and prognosis. Complete but conservative surgical removal usually results in a cure. When there is recurrence it is difficult to know if this is merely a manifestation of multifocal disease (4,7,25). Indeed, given the frequency of multifocal tumor, it is surprising that the recurrence rate is so low (26). An exceptional case of a histologically conventional canaliculal adenoma of the palate behaved aggressively and invaded into the maxillary sinus and nasal cavity (27).

Sebaceous Adenoma

Introduction. Sebaceous adenoma is defined as “a rare, usually well-circumscribed tumor composed of irregularly sized and shaped nests of sebaceous cells without cytologic atypia, often with areas of squamous differentiation and cystic change” (1).

Clinical features. Sebaceous adenoma is very rare and accounts for only 0.1% of all salivary tumors (2). It is typically seen in adults with a mean age at diagnosis of 58 years and a range of 22 to 90 years. There is a

slight male preponderance (M:F, 1.6:1) (3,4). About half of reported cases involved the parotid gland (5) with buccal mucosa (6), retromolar trigone (7), and submandibular gland in that order accounting for the remainder (4). They usually present as painless masses.

Pathology. Tumors have ranged in size from 0.4 to 3 cm in diameter and are usually circumscribed or encapsulated. The cut surface is yellow or grayish white and can be solid or cystic (3,4). Microscopically they consist of nests of cytologically bland sebaceous cells often with foci of squamous differentiation, aggregated into nests and surrounded by fibrous stroma (Figs. 71, 72). The tumor cells show positive reactivity for cytokeratin and epithelial membrane antigen but are not reactive with myoepithelial markers such as vimentin, S-100 protein, or smooth muscle actin (7). The cell nests may be microcystic, and some tumors consist mainly of dilated ductal structures with focal sebaceous differentiation.

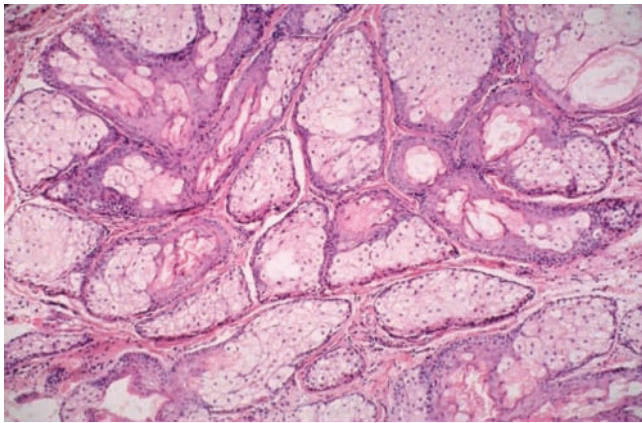


Figure 71 Sebaceous adenoma showing nests of sebaceous cells with peripheral squamous differentiation.

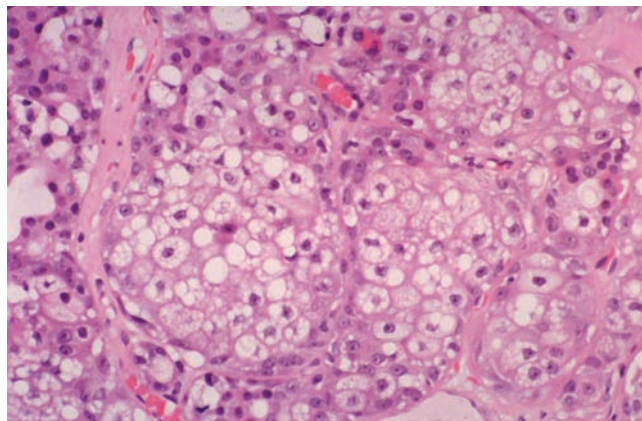


Figure 72 Sebaceous adenoma consisting solely of sebaceous cells of varying sizes.

Striking oncocytic metaplasia is occasionally seen, and there may be small areas of xanthogranulomatous inflammation (1). Very rarely, sebaceous adenomas form part of a hybrid tumor (8).

Treatment and prognosis. Sebaceous adenoma is a benign tumor that is easily eradicated by complete surgical excision.

Lymphadenomas

Lymphadenomas are rare benign salivary gland neoplasms that are histologically characterized by well-circumscribed tumors composed of proliferating epithelial nests in a lymphocytic background. In the 2005 *WHO Classification of Salivary Gland Tumors*, they were subclassified into sebaceous and nonsebaceous types, depending on the presence or absence of sebaceous differentiation (1); the former has been generally called a “sebaceous lymphadenoma” and the latter is often referred to as simply “lymphadenoma.”

Sebaceous lymphadenoma. Sebaceous cells are commonly found within normal salivary gland parenchyma, and sebaceous differentiation can be seen infrequently in a wide variety of well-recognized salivary gland tumors (2). However, primary sebaceous neoplasms arising in the salivary glands are rare and are histologically classified into sebaceous adenoma, sebaceous lymphadenoma, sebaceous carcinoma, and sebaceous lymphadenocarcinoma (2,3). The term sebaceous lymphadenoma was designated by McGavran and Bauer in 1960 (4), but a similar tumor was first described by Rawson and Horn in 1950 (5).

Clinical Features. Sebaceous lymphadenoma presents as a slowly enlarging, painless mass, almost exclusively in or around the parotid gland. One tumor occurred in the anterior midline of the neck. Slightly over 50 cases of sebaceous lymphadenoma have been reported to date (6,7). The majority of the patients are adults in the sixth to eighth decade, with an age range of 25 to 89 years (6). There is no gender predilection. Synchronous presentation with other salivary gland tumors, such as squamous cell carcinoma, acinic cell carcinoma, and Warthin’s tumor, has been reported (2).

Pathology. Grossly, the tumor appears as a well-defined and usually encapsulated mass, ranging in size from 1.3 to 6.0 cm in greatest dimension. It presents as a yellow to tan, solid, microcystic or, uncommonly, unicystic lesion on the cut surface. Sebum is commonly observed in the cystic tumor.

Microscopically, sebaceous lymphadenoma is a well-circumscribed tumor composed of uniformly distributed, variably shaped epithelial nests containing sebaceous cells, salivary duct-like structures, and cystic formations with a lymphoid background (Fig. 73). Cysts consist of numerous haphazardly arranged spaces lined by squamous, cuboidal to columnar, or sebaceous-type epithelium. Oncocytic change may be present. In addition, scattered mucous cells may also be found in ductal epithelial structures. The surrounding lymphoid stroma often shows reactive follicles with germinal centers. Foreign body giant cell reactions against the extravasated sebum are

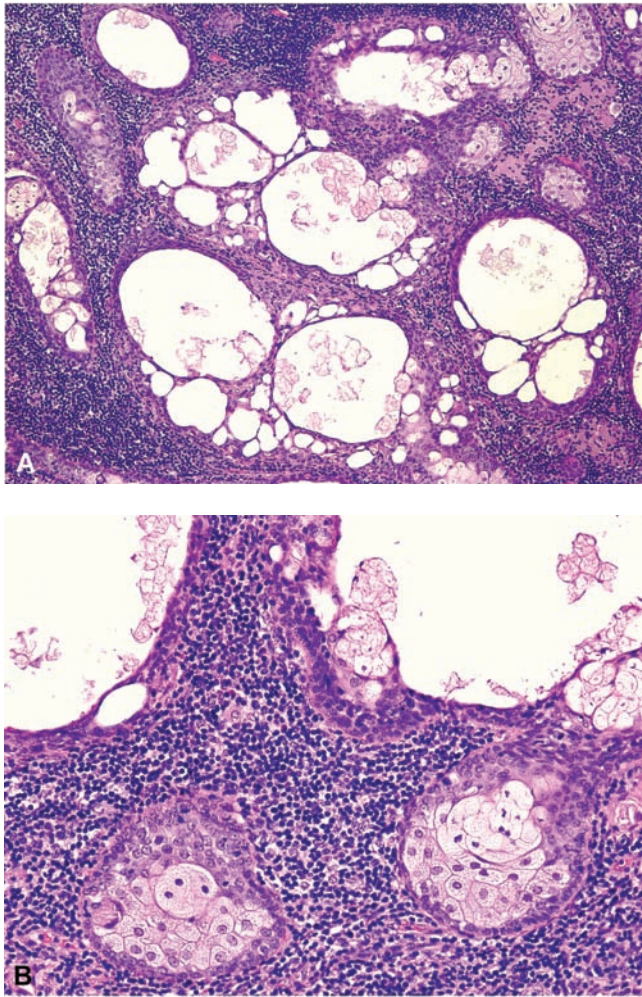


Figure 73 Sebaceous lymphadenoma. (A) Variably shaped epithelial nests with multiple cystic formations, containing sebaceous cells, in a lymphoid stroma. (B) Sebaceous glands in a diffuse lymphoid background.

common. A subcapsular marginal sinus, similar to a true lymph node, may be found in smaller tumors. Malignant transformation in sebaceous lymphadenoma, referred to as “sebaceous lymphadenocarcinoma,” is exceptionally rare, and only five such examples have been described to date (2,3).

The histogenesis of sebaceous lymphadenoma is unclear (2,8,9). One highly plausible theory is that this lesion, similar to Warthin’s tumor, arises from ectopic salivary gland inclusions entrapped in intraparotid or periparotid lymph nodes (2,8). However, another theory that the lymphoid component represents a secondary, reactive response to the epithelial proliferation, referred to as tumor-associated lymphoid proliferation (10), cannot be completely excluded in some tumors.

Differential Diagnosis. The main differential diagnoses of sebaceous lymphadenoma include low-grade mucoepidermoid carcinoma and Warthin’s

tumor. Like sebaceous lymphadenoma, low-grade mucoepidermoid carcinoma can present as a multicystic tumor with a dense lymphoid stroma. However, sebaceous lymphadenoma lacks intermediate cells and the invasive characteristics of mucoepidermoid carcinoma. Although a few mucous cells can be found in sebaceous lymphadenoma, these are restricted to the salivary duct-like epithelial cells, while clear sebaceous cells are always negative with mucin stains. Furthermore, the presence of a foreign body reaction in the lymphoid stroma, often seen in sebaceous lymphadenoma, is unusual in mucoepidermoid carcinoma (1). Oncocytic cells can be identified in sebaceous lymphadenoma, but the bilayered oncocytic epithelium and papillary-cystic configuration typical of Warthin’s tumor are absent.

Treatment and Prognosis. The treatment for sebaceous lymphadenoma is a complete surgical excision. Recurrence is exceptional and an excision with an adequate margin is curative (6).

Lymphadenoma. Lymphadenoma is a recently described, extremely rare benign salivary gland tumor consisting of an epithelial component accompanied by lymphoid stroma but lacking sebaceous differentiation (1). This tumor was first described by Auclair et al. as “cystadenoma with prominent lymphoid element” in their textbook in 1991 (6), and then four years later, they introduced lymphadenoma as a variant of sebaceous lymphadenoma (lymphadenoma that lacks sebaceous differentiation) in the Armed Forces Institute of Pathology fascicle on salivary gland tumors (9). Lymphadenoma was newly included in the 2005 *WHO Classification of Salivary Gland Tumors* (1). Some investigators speculate that lymphadenoma may be a basal cell adenoma or cystadenoma accompanied by a tumor-associated lymphoid proliferation rather than a distinct tumor entity (11).

Clinical Features. Only 10 cases have been reported in the literature (10–17). Lymphadenoma has been reported to exhibit a male predominance and the age ranges from 13 to 74 years with a mean of 48 years. Lymphadenoma occurs almost exclusively in the parotid gland. One case has been described as a preauricular mass (11). The patients typically present with a slowly growing, painless, solitary mass.

Pathology. Grossly, the tumor is a well-demarcated, solid white to gray mass, ranging in size from 1.0 to 8.0 cm in greatest dimension.

Histologically, the tumor is well circumscribed and sometimes encapsulated (Fig. 74A). It is composed of variably sized islands of epithelial cells enclosed within a prominent lymphocytic infiltrate (Fig. 74B). These features are similar to sebaceous lymphadenoma but lack sebaceous differentiation. The epithelial islands show anastomosing trabeculae, solid nests, and duct-like structures containing eosinophilic secretion, with or without cyst formation, surrounded by PAS-positive basement membrane-like material. The epithelial component may not be easily recognized due to masking by dense lymphocytic infiltrate. In such instances, PAS stain is helpful in highlighting the basement membrane-like material around the epithelial nests (1). Droplets of similar

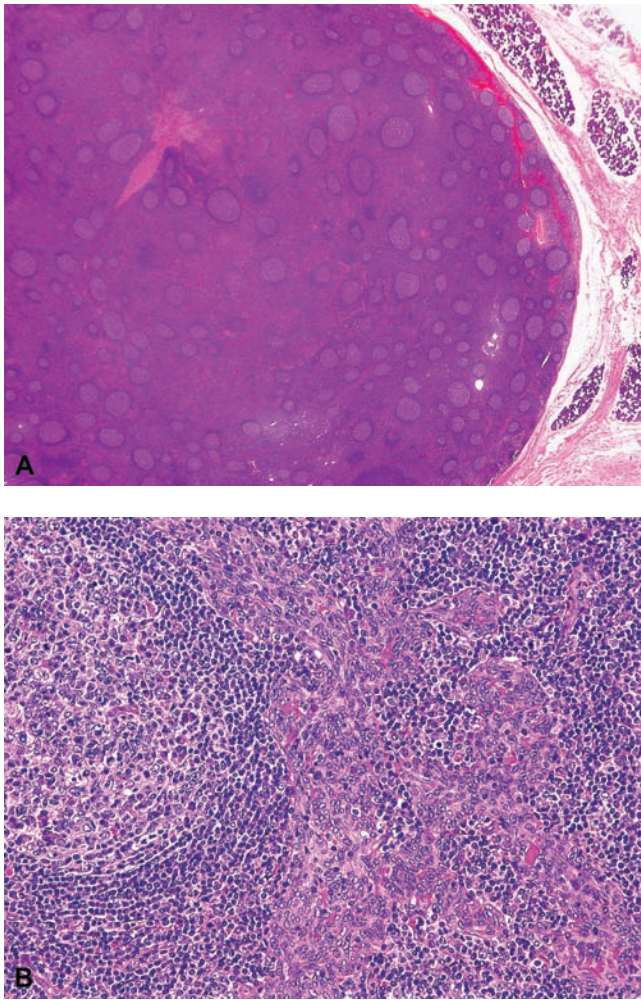


Figure 74 Lymphadenoma. (A) A well-circumscribed tumor in the parotid gland. (B) Irregularly-shaped islands of epithelial cells enclosed within a prominent lymphocytic infiltrate with lymphoid follicle. Note the lack of sebaceous differentiation.

material can also be found within tumor islands. The epithelial component consists of cuboidal to columnar cells as well as basaloid cells. These cells are usually bland but sometimes have mild atypia with vesicular nuclei and distinct, small nucleoli. Mitotic figures are rare. Neither sebaceous nor oncocytic cells have been identified. The lymphoid stroma, which is generally considered to represent tumor-associated lymphoid proliferation (10), consists of small mature lymphocytes often accompanied by lymphoid follicles with germinal centers. The subcapsular sinuses seen in lymph nodes are not observed.

Immunohistochemistry. Immunohistochemical findings indicate dual luminal cell and abluminal cell differentiation without myoepithelial cell participation in the epithelial elements of lymphadenoma. The luminal cells are positive for epithelial membrane antigen and low-molecular weight cytokeratin, whereas the abluminal cells are immunoreactive for p63 but

negative for smooth muscle actin (11). The lymphoid cells comprise a mixture of B cells and T cells. In situ hybridization for EBER is negative in both epithelial tumor cells and infiltrating lymphoid cells (11).

Differential Diagnosis. The main differential diagnoses of lymphadenoma include lymphoepithelial sialadenitis (LESA), metastatic adenocarcinoma in lymph nodes, lymphoepithelial carcinoma, and acinic cell carcinoma with a tumor-associated lymphoid tissue. Unlike LESA, lymphadenoma forms a well-circumscribed lesion. In addition, the epithelial component in lymphadenoma is proliferative and much more prominent than epimyoeplithelial islands in LESA. Metastatic adenocarcinoma in the lymph nodes can be distinguished from lymphadenoma by the presence of definite nuclear atypia and lymph node structure. The most important differential diagnosis of lymphadenoma is lymphoepithelial carcinoma. Since cellular atypia in lymphoepithelial carcinoma may be mild, cellular features alone may not be enough to allow differentiation from lymphadenoma. Features such as lack of mitotic activity, lack of invasive growth with desmoplastic stroma, presence of ductal differentiation, and negativity for EBER in situ hybridization favor a diagnosis of lymphadenoma rather than lymphoepithelial carcinoma. Acinic cell carcinoma is sometimes accompanied by a dense lymphoid stroma that can pose difficulty in the differential diagnosis of lymphadenoma. However, in acinic cell carcinoma the lymphoid component is usually more prominent in the peripheral portion. Additionally, the epithelial component of lymphadenoma does not show a microcystic growth pattern and lacks cells possessing diastase-resistant PAS-positive zymogen secretory granules.

Treatment and Prognosis. Complete surgical excision is the choice of the treatment for lymphadenoma. No recurrences have been reported.

Ductal Papillomas

Although many salivary gland tumors arise from ductal units and exhibit papillary configuration, benign papillary tumors confined to the ducts are rare. They are largely categorized under the term "ductal papillomas" and generally further classified as three distinct types of tumors: intraductal papilloma, sialadenoma papilliferum, and inverted ductal papilloma (1,2). These tumors occur predominantly in the intraoral minor salivary glands and develop in association with the salivary excretory duct system.

Intraductal papilloma. Intraductal papilloma is histologically characterized by papillary proliferations of bland cuboidal-to-columnar epithelial cells; the proliferations have fibrovascular cores and protrude into the cystically dilated ductal space (1,2).

Slightly over 40 cases of intraductal papilloma have been reported to date (3–11). This rare tumor mostly occurs in the minor salivary glands and only a few have been described in the major salivary glands (1). Of the minor salivary gland cases, the lips followed by the buccal mucosa and palate are the most frequent sites (9). In the major salivary glands, the

parotid gland is the most common site, but development in the submandibular and sublingual glands has also been reported (8,9). Clinically, the patients typically present with a painless oral submucosal mass. The majority of the patients are in their sixth or seventh decades with a mean age of 63 years (9). Men and women are affected almost equally.

Grossly, the cut surface of the tumor reveals a unilocular cystic lesion somewhat removed from the mucosal surface. Tumor size ranges from 0.5 to 2.0 cm (2).

Microscopically, there is a cystically dilated duct with papillary epithelial projections into the cystic space; each projection is composed of a branching and anastomosing proliferation of a single or double layer of high columnar epithelial cells, with a fibrovascular core (Fig. 75). The tumor cells show no proliferation beyond the cyst wall. They have uniform and basally located nuclei with no evidence of atypia. A few PAS- and Alcian blue-positive mucous cells are seen. There are few mitotic figures. The cystic lesion is usually surrounded by thick fibrous tissue.

Intraductal papilloma has immunohistochemical properties of ductal luminal cells (5,8). The tumor cells express pan-cytokeratin and epithelial membrane antigen but are negative for smooth muscle actin and the Ki-67 labeling index is low (8).

Before establishing a diagnosis of intraductal papilloma, it is necessary to rule out several papillary and cystic salivary gland tumors, including papillary cystadenoma, low-grade cribriform cystadenocarcinoma (LGCCC) (formerly referred to as "low-grade salivary duct carcinoma") (12), and the papillary-cystic variant of acinic cell carcinoma (2).

Papillary cystadenoma is characterized by a benign neoplastic papillary proliferation of salivary gland duct epithelium in the form of multiple epithelial-lined cystic structures. Papillary cystadenoma does not involve the native duct system, whereas intraductal papilloma proliferates within a cystically dilated duct and does not form cysts separated from the duct system. LGCCC is characterized by multiple ductal in situ lesions with micropapillary, tufted, and plaque-like intraluminal projections, rather than frank papillary projections with fibrovascular cores protruding into a cystically dilated duct (12). Acinic cell carcinomas rarely show prominent papillary and cystic features; they predominantly have a proliferating epithelium resembling intercalated ductal cells admixed with acinar cells at least focally. Usually, the papillary-cystic variant of acinic cell carcinoma shows a more delicate fibrovascular core, if present, and occasionally contains a microcystic or follicular structure, a feature absent in intraductal papilloma. The lack of acinar differentiation, as well as the negative granular staining pattern of the tumor cells with PAS/D stain, helps to exclude the possibility of acinic cell carcinoma.

Excision is curative without recurrence having been reported. One case each of the malignant counterpart of the intraductal papilloma (intraductal papillary carcinoma with an invasive component) and

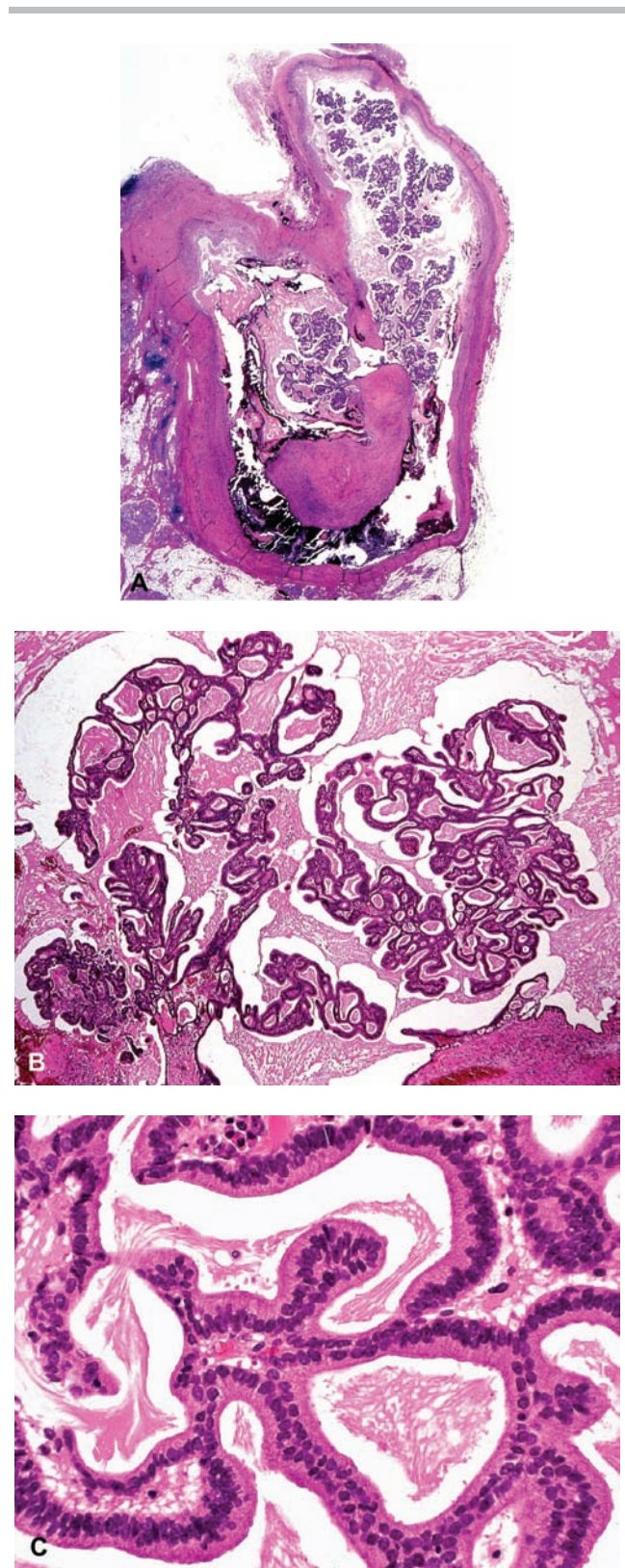


Figure 75 Intraductal papilloma. (A) A cystically dilated duct with papillary epithelial projections into the cystic space. (B) A projection is composed of a branching and anastomosing proliferation of epithelial cells with a fibrovascular core. (C) Columnar tumor cells have uniform and basally located nuclei with no evidence of atypia.

papillary adenocarcinoma possibly arising from an intraductal papilloma has been described (6,8).

Sialadenoma papilliferum. Sialadenoma papilliferum is characterized by a biphasic growth pattern of exophytic squamous and endophytic glandular components, closely resembling syringocystadenoma papilliferum of the skin (1,2).

Since it was first described by Abrams and Finck in 1969 (13), slightly less than 50 cases have been reported in the literature (9,13–25). The incidence of sialadenoma papilliferum is approximately 1% of all minor salivary gland tumors, and almost all of them affect intraoral minor salivary glands, mostly the palate (9). Other intraoral sites include the buccal mucosa, upper lip, retromolar pad, and pillars of fauces (1). It has also been reported in the esophagus and bronchus (18,21). The age of the patients ranges from 18 to 87 years with a mean of 59 years (1). Men are slightly more commonly affected. Clinically, the lesion presents a painless, exophytic papillary growth from the surface of the mucosal epithelium and is often mistaken for squamous papilloma.

Grossly, the cut section of the tumor reveals a well-defined, exophytic lesion with papillary or verrucous structures in the center. The size generally ranges from 0.3 to 2.0 cm with a mean of 0.7 cm (9).

Histologically, at low magnification, the lesion shows biphasic exophytic and endophytic growth patterns around the orifice of the excretory duct close to the oral mucosal surface (Fig. 76A). The exophytic component projecting above the mucosal surface is composed of papillary proliferations of well-differentiated stratified squamous epithelium enclosing fibrovascular cores. At the deeper portion of the exophytic lesion, the stratified squamous papillary projections merge into ductal epithelial proliferation displaying an irregular outline along a dilated excretory duct with infolding in the glandular structures (Fig. 76B). On higher magnification, the stratified squamous epithelium in the exophytic portion is hyperplastic with hyperkeratosis, parakeratosis, and focal hypergranulosis. The ductal epithelium consists of a distinct double layer of outer cuboidal and inner columnar cells. Scattered mucous cells can also be seen. The supporting fibrovascular cores often contain numerous plasma cells with a few lymphocytes.

Immunohistochemical studies suggest that sialadenoma papilliferum exhibits both ductal and myoepithelial differentiation (17,20,22). The luminal columnar cells of the ductal structures express pancytokeratin, carcinoembryonic antigen, and epithelial membrane antigen, whereas the basally located cells show immunoreactivity for vimentin, cytokeratin 14, and smooth muscle actin. Polymerase chain reaction examination failed to detect human papillomavirus DNA in sialadenoma papilliferum (19).

The characteristic histological features of sialadenoma papilliferum with a biphasic pattern with an exophytic and endophytic proliferation may pose some problems in the histologic diagnosis. The differential diagnosis includes squamous papilloma, verrucous carcinoma, papillary cystadenoma, inverted ductal papilloma, and mucoepidermoid carcinoma (2,9).

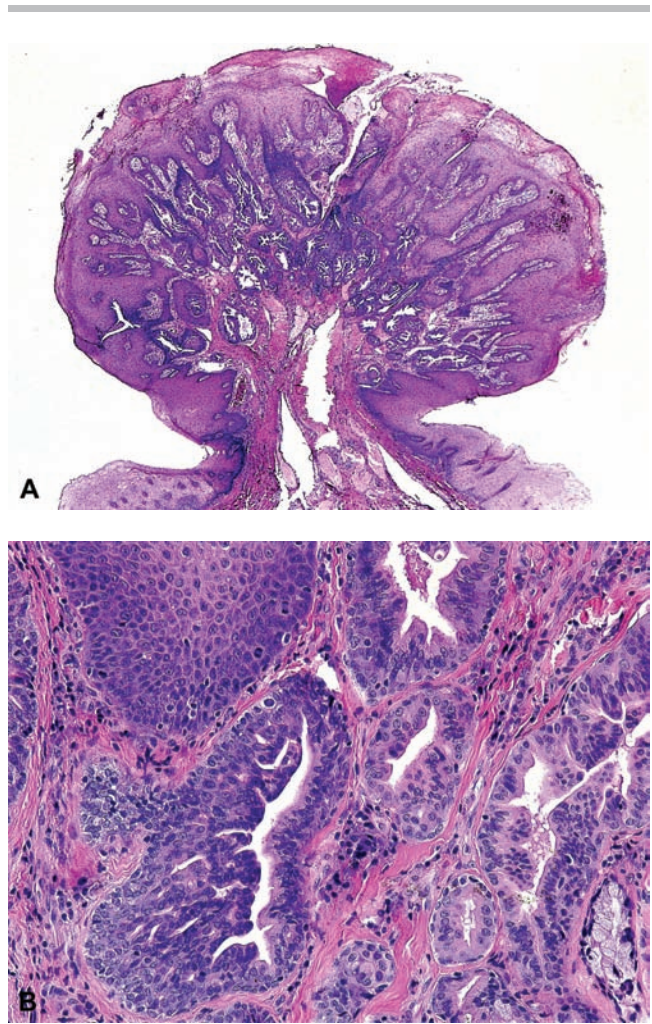


Figure 76 Sialadenoma papilliferum. (A) A well-defined, pedunculated lesion with biphasic exophytic and endophytic growth patterns around the orifice of the excretory duct close to the oral mucosal surface. (B) Papillary proliferations of the lesion are composed of both well-differentiated stratified squamous epithelium and a double layer of ductal epithelium.

Squamous papilloma and verrucous carcinoma are composed exclusively of a squamous component and lack the deeper ductal proliferation of sialadenoma papilliferum. Papillary cystadenoma shows duct cell lining multicystic structures similar to the deeper portion of sialadenoma papilliferum but does not have an exophytic component consisting of papillary proliferation of squamous cells. Unlike sialadenoma papilliferum, inverted ductal papilloma is characterized by an entirely endophytic growth without ductal proliferation. In sialadenoma papilliferum, the biphasic patterns of exophytic squamous component and endophytic ductal component are distinct, while a mixture of squamous, mucous, and intermediate cells is a typical feature of mucoepidermoid carcinoma.

Careful and complete surgical excision is the recommended treatment for sialadenoma

papilliferum, because it has a high (10–15%) risk of postoperative recurrence (1,16). This is in contrast to intraductal papilloma and inverted ductal papilloma, which are nonrecurrent tumors. One case of malignant transformation into epithelial-myoepithelial carcinoma and high-grade invasive micropapillary carcinoma from sialadenoma papilliferum has been reported (23). Recently, a case of sialadenoma papilliferum with epithelial dysplasia and carcinoma in situ in the exophytic component has also been described (24).

Inverted ductal papilloma. The term “inverted ductal papilloma” of minor salivary glands was initially proposed in 1982 by White et al. for a tumor histologically resembling inverted papilloma of the sinonasal tract (26). In contrast to the nasal inverted papilloma, which arises from the surface epithelium, inverted ductal papilloma develops at the junction of the salivary excretory duct and the oral mucosal epithelium.

Inverted ductal papilloma is the rarest form of the ductal papillomas. Slightly more than 30 cases have been reported to date, arising exclusively in the minor salivary glands (9,26–31). The lip and buccal mucosa are more frequently involved, but this tumor less commonly arises at other oral sites including the palate and the floor of the mouth (9). Inverted ductal papilloma has a slight male predominance. The age ranges from 28 to 77 years, with a mean age of over 50 years (9). Clinically, inverted ductal papilloma presents as a painless, submucosal, nodular swelling, often with a central punctum.

Grossly, the lesions form a well-circumscribed mass, with occasional cystic change, communicating with the oral mucosal surface. Tumor size ranges from 0.5 to 1.5 cm with an average of 0.9 cm (9).

Microscopically, the lesion is located at or near the orifice of salivary excretory ducts and is sharply demarcated from the adjacent lamina propria. It appears as a dilated duct of a minor salivary gland filled with papillary structures supported by fibrovascular cores (Fig. 77A). It is lined by a thick layer of predominantly nonkeratinizing stratified squamous and basaloid epithelium with numerous invaginations and cleft-like narrow spaces (Fig. 77B). The proliferating tumor epithelium is continuous to the surface epithelium. The papillary fronds contain cuboidal or columnar duct cells with occasional mucous goblet cells and microcysts. The epithelial cells do not have atypia, and mitotic figures are rare.

Immunohistochemical investigations indicate that the origin of inverted ductal papilloma is in the excretory ductal cells of minor salivary glands (28). The tumor cells react with pan-cytokeratin, epithelial membrane antigen, and carcinoembryonic antigen. S-100 protein, vimentin, and smooth muscle actin are negative. The presence of human papillomavirus DNA using in situ hybridization has been reported in the tumor (29).

Inverted ductal papilloma should be differentiated from other intraoral minor salivary gland tumors, especially sialadenoma papilliferum and mucoepidermoid carcinoma (2,9). Unlike the exophytic growth of inverted ductal papilloma, sialadenoma papilliferum exhibits biphasic exophytic and endophytic components. The

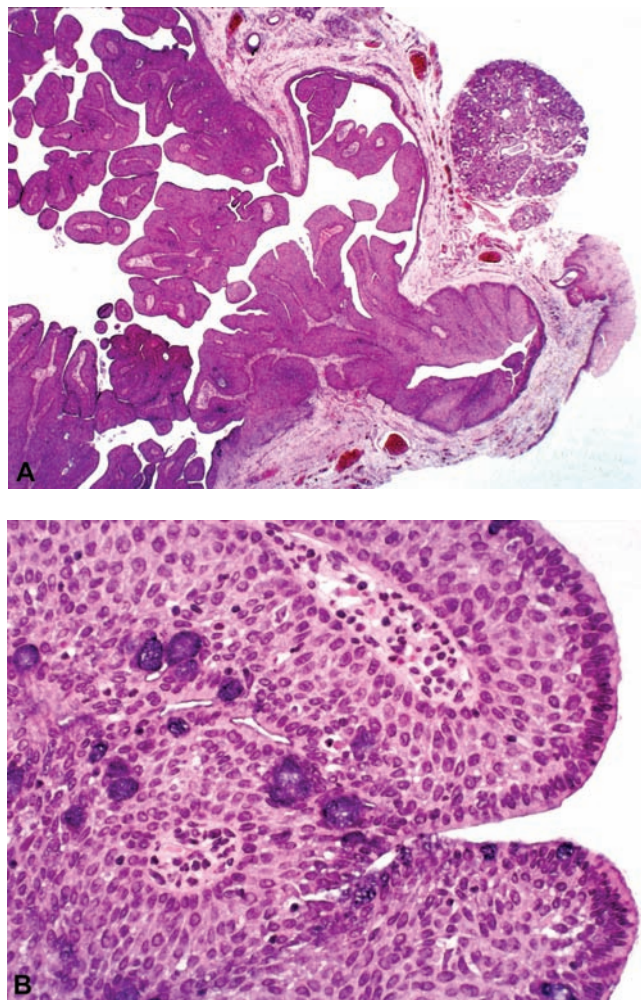


Figure 77 Inverted papilloma. (A) A dilated duct of the minor salivary gland filled with papillary structures. (B) High magnification of papillary proliferations reveals a thick layer of predominantly non-keratinizing stratified squamous and basaloid epithelium. The papillary fronds contain columnar duct cells with occasional mucous goblet cells.

latter component consists of a proliferation of ductal epithelium but not squamous and basaloid epithelium of inverted ductal papilloma. Mucoepidermoid carcinoma is the most important lesion to be distinguished from inverted ductal papilloma, because they both have squamous and mucous goblet-type cells. Inverted ductal papilloma lacks intermediate cells and the invasive growth characteristic of mucoepidermoid carcinoma.

Simple excision is the choice of treatment. Recurrence or malignant transformation has not been reported (9).

Cystadenoma

Introduction. Cystadenoma is defined as “a rare benign epithelial tumor characterized by predominantly multicystic growth in which the epithelium

demonstrates adenomatous proliferation. The epithelial lining is frequently papillary and rarely mucinous" (1). Previously, some investigators interpreted this lesion to be reactive cystic hyperplasia of the salivary gland duct rather than a true neoplasm and used corresponding terms such as "duct ectasia," "salivary duct cyst," and "intraductal papillary hyperplasia" (2,3). However, now cystadenoma is generally believed to be neoplastic because of its proliferative properties (2).

Clinical features. The incidence of cystadenoma varies from 1.2% to 6.3% of all intraoral minor salivary gland neoplasms (4-7), and it accounts for 4.1% of all benign epithelial salivary gland tumors based on the large files of the AFIP (3). These tumors represent 7% and 3.1% of minor and major salivary gland neoplasms, respectively (3). Patient ages range from 12 to 89 years, with a mean of about 57 years (3). There is a female predominance of between 2:1 and 3:1 (3,4,7). The major and minor salivary glands are almost equally involved. In the major salivary glands, cystadenoma occurs frequently in the parotid gland (45%), followed by the submandibular gland (7%) (3). The lips and buccal mucosa are the most frequent locations for this tumor in the intraoral minor salivary gland sites (3,4). The palate is less commonly involved compared with other minor salivary gland tumors. Cystadenoma can also arise in the larynx or in the sinonasal tract (8,9).

Cystadenoma typically presents as a slow-growing, painless mass, usually less than 1 cm in greatest dimension when arising in the minor salivary glands. The clinical appearance is similar to a mucocele.

Pathology. Grossly, cystadenoma is a well-circumscribed tumor with multiple small cystic spaces or rarely a single large cyst formation on the cut surface.

Microscopically, the tumor is usually composed of variably sized, multiple cysts with or without a fibrous capsule (Fig. 78A). Each cystic space is separated by limited, dense, fibrous stroma. Although papillary configurations are commonly seen in this tumor, the term "papillary cystadenoma" is applied only when the lesion has multilocular cyst formations with conspicuous multiple papillary projections into the cystic spaces (10,11). Cyst formation may appear as a single space in cystadenoma, but unicystic lesions with intracystic papillary proliferations with fibrovascular cores should be included in the category of intraductal papilloma rather than unicystic cystadenoma. The cysts contain eosinophilic, proteinaceous material, sometimes with a few epithelial and inflammatory cells. Psammoma bodies or crystalloids (tyrosine-rich crystals) are rarely present within the luminal secretions (12,13). The cyst-lining epithelium consists of mostly cuboidal or columnar cells (Fig. 78B). Mucous, oncocytic, squamous, and apocrine cells are also present in the epithelium focally or occasionally extensively; a mixture of several cell types may commonly be seen. In "mucinous cystadenoma," multiple cysts are predominantly lined by mucous columnar epithelium.

"Oncocytic cystadenoma" is composed of papillary-cystic proliferation of a single- or double-layered oncocytic epithelium, superficially resembling a

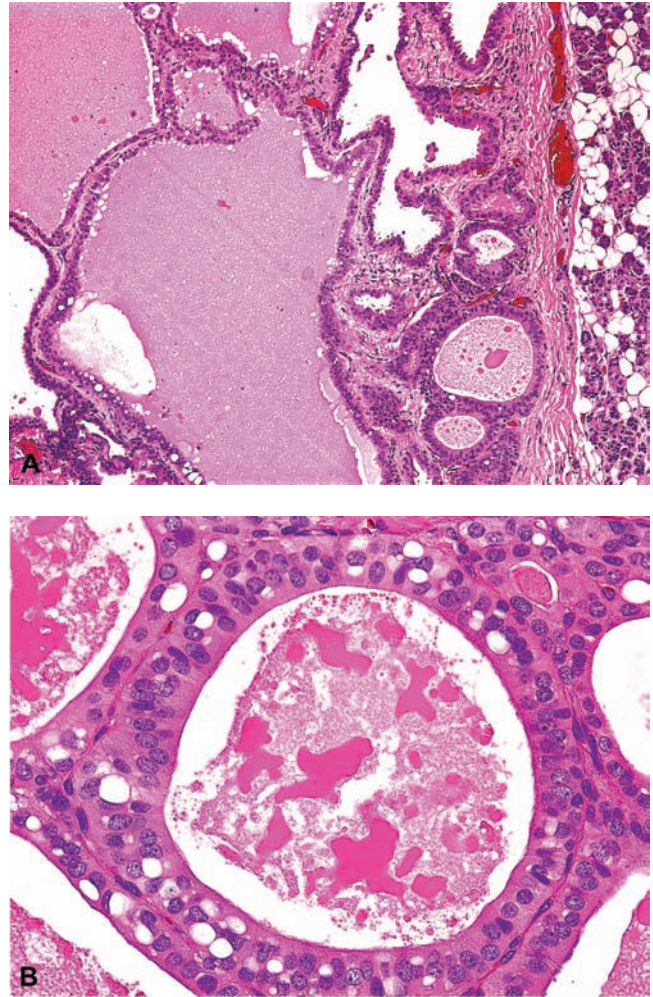


Figure 78 Cystadenoma. (A) Well-circumscribed tumor composed of variably sized, multiple cysts with focal papillary configurations. (B) The cyst lining epithelium consists of columnar or cuboidal cells. The cysts contain eosinophilic, proteinaceous material.

Warthin's tumor without lymphoid stroma (Fig. 79) (3,14). The oncocytic epithelial cells are stained by phosphotungstic acid hematoxylin, and their cytoplasm strongly reacts with an antimitochondrial antibody (14). One oncocytic cystadenoma had a prominent signet-ring cell component (15). Lining epithelial cells have no cellular atypia, and mitoses are rare. The thickness of the lining epithelium may vary between cases or within a single tumor, but cystadenoma usually lacks an extraluminal, solid epithelial component. Foci of lymphocytic cell aggregations are sometimes evident in the fibrous stroma.

Differential diagnosis. The main differential diagnoses include salivary duct cyst, duct ectasia due to obstruction, polycystic (dysgenetic) disease, Warthin's tumor, low-grade mucoepidermoid carcinoma, the papillary-cystic variant of acinic cell carcinoma, and cystadenocarcinoma.

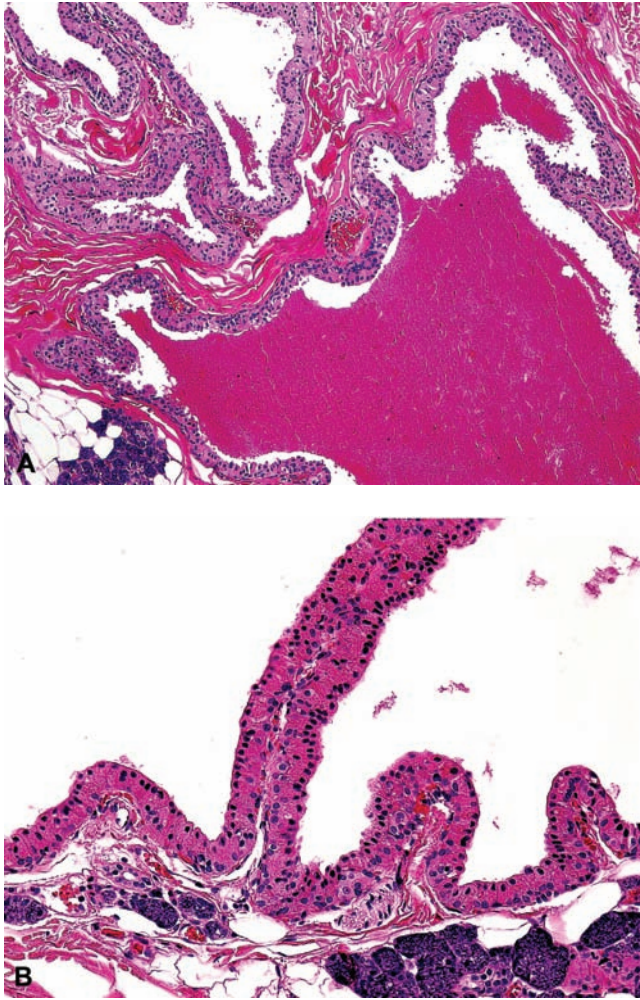


Figure 79 Oncocytic cystadenoma. (A) Papillary-cystic proliferation of oncocytic epithelium in the parotid gland. Note the absence of lymphoid infiltration in fibrous stroma separating cystic spaces. (B) The cysts are lined by a double-layered oncocytic epithelium, resembling that seen in Warthin tumor. Source: Courtesy of Dr. Jean E. Lewis, Mayo Clinic, Rochester, Minnesota, U.S.A.

Salivary duct cyst is a unilocular lesion lined by a smoothly outlined epithelium without intracystic papillary proliferations. Duct ectasia secondary to obstruction often displays a multicystic appearance, but this lesion involves several duct segments usually associated with acinar atrophy, fibrosis, and chronic inflammatory cell infiltration in the adjacent salivary gland. Unlike the well-circumscribed tumor formation of cystadenoma, polycystic disease is a diffuse lesion throughout the affected salivary gland.

The oncocytic variant of papillary cystadenoma lacks a dense lymphoid stroma characteristic of Warthin's tumor. Additionally, the lining epithelium of oncocytic cystadenoma may focally be admixed with cuboidal or columnar cells. Multicystic and papillary pattern of low-grade mucoepidermoid carcinoma can

mimic cystadenoma. However, solid nests composed of a mixture of epidermoid, mucous, and intermediate cells characteristic of mucoepidermoid carcinoma are absent in cystadenoma. The papillary-cystic variant of acinic cell carcinoma can be difficult to distinguish from cystadenoma. In acinic cell carcinoma, at least some cells containing diastase-resistant PAS-positive zymogen secretory granules can be identified in the proliferating epithelium. In addition, characteristic microcystic growth patterns may be seen in the intraluminal papillary fronds in acinic cell carcinoma. Cystadenocarcinoma usually has obvious cellular atypia and shows invasive growth into surrounding salivary gland parenchyma (16). The overall appearance of low-grade cribriform cystadenocarcinoma (LGCCC) (17), originally called low-grade salivary duct carcinoma (18), is very similar to that of cystadenoma. However, LGCCC is a purely intraductal carcinoma lesion.

Treatment and prognosis. Complete surgical excision with a good safety margin is the choice of treatment for cystadenoma. Although recurrence after appropriate treatment is rare and the prognosis is excellent, a case of malignant transformation to invasive micropapillary adenocarcinoma from mucinous cystadenoma has been reported (19).

Keratocystoma

Introduction. Squamous cells are known to be present in a variety of salivary gland diseases. However, benign salivary gland tumors composed of purely squamous cells are quite unusual. Keratocystoma is a rare, benign salivary gland tumor characterized by multicystic spaces lined by stratified squamous epithelium containing keratotic lamellae and focal solid epithelial nests (1,2). In 1999, Seifert et al. reported the first example of this tumor, which they called "choristoma," resembling trichoadenoma (1). In 2002, Nagao et al. described two histologically identical cases and designated them "keratocystoma," a term that refers to the specific histopathologic features of the tumor (2). In the 2005 *WHO Histological Classification of Salivary Gland Tumors*, keratocystoma was not adopted as an independent entity, and instead was briefly mentioned in the section of squamous cell carcinoma (3).

Clinical features. Only three cases of keratocystoma have been reported (1,2). The patients, two males and one female, were from 8 to 38 years old. However, increased recognition of the tumor may alter the epidemiologic characteristics. All three reported tumors arose in the parotid gland. Clinically, the tumor manifests as a painless, slowly growing mass in the parotid gland. CT shows a low-density multilocular cystic mass with enhanced septa. Keratocystoma is a completely benign tumor. After subtotal parotidectomy, no additional therapy is needed.

Pathology. The cut surface of the tumor shows a multilocular cystic lesion filled with a keratin-like substance (Fig. 80A). The three reported tumors had a maximum dimension of 1.3 to 4.0 cm.

Histopathologically, the tumor consists mainly of multiple cysts that contain keratotic lamellae

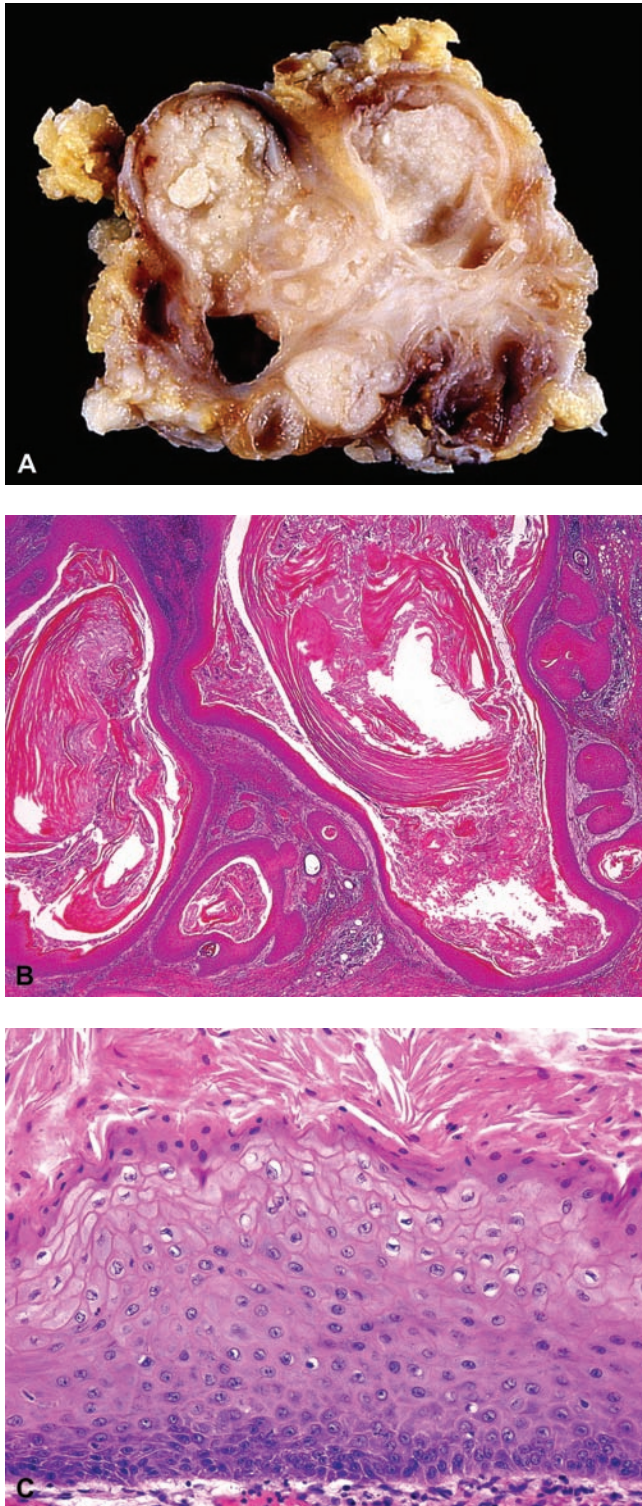


Figure 80 Keratocystoma. (A) Cut surface of the parotid tumor, showing multiple cystic formations filled with keratin material. (B) Low-power view showing multilocular cystic lesions filled with lamellar keratin material. (C) Portion of the cyst wall consists of stratified squamous epithelium with keratinization through parakeratotic cells. Note the lack of a granular cell layer. Tumor cells exhibit uniform, bland nuclei and abundant eosinophilic cytoplasm.

(Fig. 80B). Stratified squamous epithelium lines the cystic spaces and shows a parakeratotic or orthokeratotic surface without a granular cell layer (Fig. 80C). The stratification of the epithelium is oriented regularly from the outer basal to the inner keratotic cell layers. Focally, the outer layer demonstrates budlike protrusions. In some areas, solid squamous cell islands with sharply defined margins are surrounded by collagenous stroma. The tumor does not have a definite lobular architecture. The solid areas of squamous cell nests are localized partly within the parenchyma of the parotid gland adjacent to an excretory duct and should not be interpreted as invasive growth. Cells of the neoplastic squamous epithelium have uniform, bland nuclei, and abundant eosinophilic cytoplasm. There is no oncocytic or mucous cell differentiation. The few scattered mitotic figures are limited to the outer epithelial layer. The transformation from parotid ductal epithelium to neoplastic cells through a squamous-metaplasia-like process may be evident. Foci of giant cell reaction against extravasated keratin may be apparent.

Squamous differentiation of the tumor cells is confirmed by immunohistochemical stains positive for cytokeratins by AE1/AE3 and cytokeratin 14 but negative for cytokeratins 8 and 18 (2). Staining for smooth-muscle actin and S-100 protein is negative. Ki-67 immunoreactive cells may be limited to the area along the outer basal layer of the neoplastic epithelium. Collagen type IV-positive material surrounds the epithelium lining the cysts and the solid cell nests.

Differential diagnosis. Several salivary gland tumors and tumor-like lesions containing squamous cells should be ruled out before the diagnosis of keratocystoma, including primary and metastatic squamous cell carcinomas, mucoepidermoid carcinoma, squamous metaplasia in certain benign neoplasms and conditions, and cysts (2). Primary squamous cell carcinoma of the parotid gland is an aggressive malignancy with frequent facial nerve involvement or cervical metastases (3). Cystic changes are a well-known finding in metaplastic nodal squamous cell carcinomas and are also noted in primary squamous cell carcinoma of the parotid gland. In keratocystoma, the consistent absence of metastasis, necrosis, invasion, and perineural or intravascular growth, as well as the lack of cytological atypia and minimal cell proliferative activity, weighs against malignancy. The solid areas of squamous cell formation partly localized within the parotid gland parenchyma in the vicinity of an excretory duct should not be interpreted as invasive growth. In addition to the benign characteristics described above, the absence of incorporated mucous cells and the presence of marked keratinization are important for distinguishing this tumor from mucoepidermoid carcinoma.

Squamous metaplasia is known to occur in several benign salivary gland tumors. In pleomorphic adenoma, squamous elements usually coexist with variable myxochondromatous, myoepithelial, or glandular components. Warthin's tumors sometimes show areas of squamous metaplasia, for example, in metaplastic (infarcted) Warthin's tumor (4,5). These

areas, however, are usually accompanied by extensive necrosis, and immunoreactivity for cytokeratins may reveal columnar cell phenotypes but no squamous differentiation (5). In addition, foci with characteristic double cell layer of oncocytic cells are present at least focally even in such type of Warthin's tumor.

Other lesions that can be mistaken for keratocystoma are necrotizing sialometaplasia and epidermal and dermoid cysts. Necrotizing sialometaplasia is an inflammatory and usually self-limiting disorder of the salivary glands that occurs commonly in the hard or soft palate but can also be found in the parotid gland (6–8). In keratocystoma, the lack of the lobular infarction or necrosis and the general lobular morphology, the formation of much larger cysts, and the absence of a granular layer in the squamous lining may be helpful for distinguishing it from necrotizing sialometaplasia. Rarely, epidermal and dermoid cysts may occur in the parotid gland (9,10). Most epidermal cysts show unilocular cystic formation with a granular layer in their lining. Unlike in dermoid cysts, skin appendages such as hair follicles and sebaceous glands are absent in keratocystoma.

I. Malignant Tumors

Acinic Cell Carcinoma

Introduction. Acinic cell carcinoma is defined as “a malignant epithelial neoplasm of salivary glands in which at least some of the neoplastic cells demonstrate serous acinar differentiation, which is characterized by cytoplasmic zymogen secretory granules. Salivary ductal cells are also a component of this neoplasm” (1). Synonyms include acinic cell adenocarcinoma and acinous cell carcinoma.

Clinical features. Acinic cell carcinoma accounts for about 3% to 6% of all salivary gland tumors and between 7% and 17.5% of malignant salivary neoplasms in major series (2–5). The parotid gland is the most common site accounting for about 80% to 90% of cases (2), with tumors of the minor glands of the oral cavity forming the second most common site (2,5). Intraoral tumors are most frequent in the upper lip, buccal mucosa, and palate. Acinic cell carcinoma is relatively uncommon in the submandibular gland (~4%) and rare in the sublingual gland (2). Occasional cases are reported in the lacrimal gland (6) and seromucous glands of the upper and lower respiratory tract (7,8). Central tumors in the mandible have also been described (9). It is the most common malignant salivary gland tumor to arise bilaterally (3%) (10,11). Acinic cell carcinoma may be a component of a hybrid tumor (12).

There is a slight female predominance in most published series (2,4,13–15), and tumors are seen over a wide age range (3–91 years) with a fairly uniform age distribution from the third to seventh decades (2). The mean age in the largest series was 44 years (2). It is the second most common salivary malignancy in children (16–19). There is no ethnic predilection, and there are only two case reports suggesting a familial association (11,20).

Acinic cell carcinoma usually presents as a slow-growing, painless, mobile mass, although some cases may be fixed and nodular. The duration ranges from a few weeks to over 40 years with an average of 6 to 7 years (2,15,21–23). Pain or tenderness is present in about half of the cases and facial nerve involvement is seen in 5% to 10% of patients (15,22,24,25).

Pathology. Grossly, tumors form rubbery or firm, round or lobulated, circumscribed masses that are usually less than 3 cm in diameter. A minority of tumors have ill-defined margins or appear multifocal. The cut surfaces vary from white to yellow to tan and red. They may be homogeneous or show extensive cystic change. Recurrent tumors form multifocal and often poorly defined nodules.

Microscopically, there is a surprisingly wide range of cell types and architectural configurations with a unifying feature of serous acinar differentiation in some part of the tumor. The cell types present, other than serous acinar cells, include intercalated ductal, nonspecific glandular, vacuolated, and clear cells. Acinar cells (Fig. 81) are the commonest and most characteristic cells. They resemble the normal serous acinar cells and are round or polyhedral and have abundant, pale, basophilic cytoplasm. These contain dense, grayish, or blue zymogen granules that may be fine or moderately coarse and are PAS positive and diastase resistant (Fig. 82). The nuclei are round, uniform, and typically located peripherally. They are usually darkly stained and basophilic or occasionally more vesicular. Intercalated duct-type cells are smaller, cuboidal in shape, and have less cytoplasm that, in contrast, is eosinophilic or amphophilic. The nuclei are usually centrally located. These cells surround duct-like spaces of variable sizes. Vacuolated cells are a common and sometimes conspicuous component of the tumor (26). They contain clear, PAS/D-negative cytoplasmic vacuoles of variable sizes or, less frequently, occasional zymogen granules can also be identified. The nuclei have an open chromatin pattern and may show more pleomorphism than acinar or

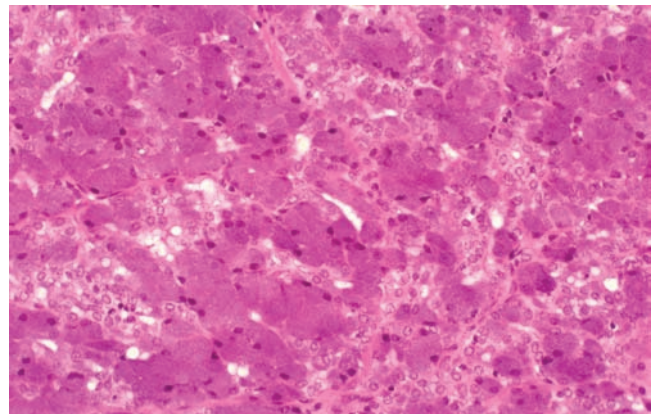


Figure 81 Acinic cell carcinoma showing basophilic, granular cells that resemble normal serous acinar cells.

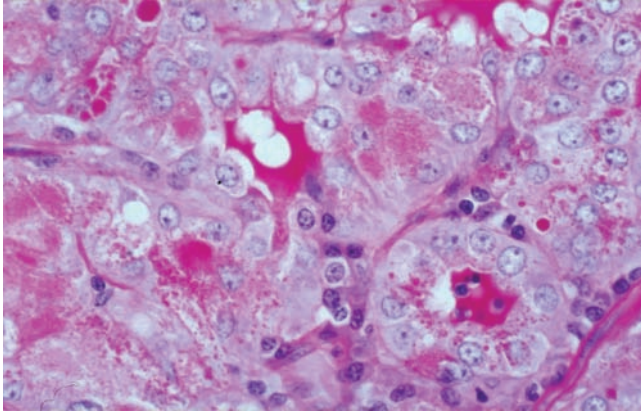


Figure 82 Acinic cell carcinoma. Periodic acid Schiff stain highlighting zymogen granules on the luminal aspect.

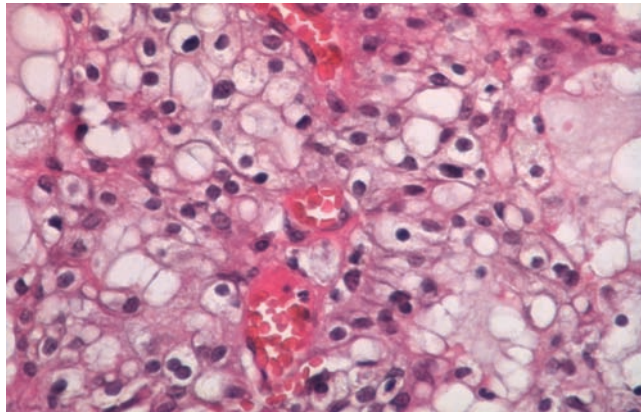


Figure 83 Acinic cell carcinoma showing focal clear cell change.

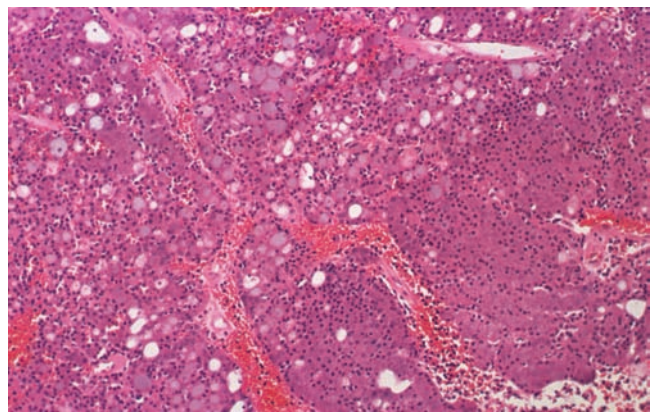


Figure 84 Acinic cell carcinoma with solid and microcystic pattern.

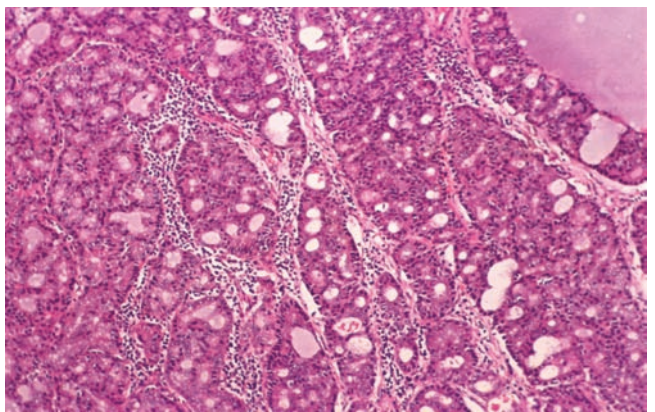


Figure 85 Acinic cell carcinoma with microcystic pattern and lymphocyte-rich stroma.

intercalated ductal cells. Cells that have clear cytoplasm and conspicuous cell membranes are seen singly or in small foci. They do not contain glycogen and in some cases may be a fixation or processing artifact (Fig. 83) (21,27). They are seen in only 6% of acinic cell carcinomas (15). Nonspecific glandular cells are round or polygonal and are smaller than acinar cells. They have amphophilic cytoplasm and aggregate as sheets of cells with indistinct cytoplasmic borders. The nuclei are larger and more vesicular than in the other cell types and in addition are more likely to show pleomorphism and mitotic figures.

Acinic cell carcinomas show a variety of growth patterns that include solid, microcystic, papillary-cystic, and follicular, and tumors may contain one or several of these architectural subtypes. This morphologic diversity, together with the heterogeneity of the cellular component, contributes to the widely variable histologic appearances of this tumor. In the solid type,

the tumor usually consists of sheets or nodules of closely aggregated, cytologically bland acinar cells and sometimes smaller numbers of nonspecific glandular cells or intercalated ductal cells (Fig. 84). The microcystic pattern is the most common subtype and numerous small spaces within the tumor give it a lattice-like pattern (Fig. 85). In addition to the serous acinar cells, this variant often contains significant numbers of intercalated ductal cells and vacuolated cells. In some cases the cystic spaces enlarge, and there is papillary intracystic proliferation (Fig. 86A,B). In this papillary-cystic variant, cells on the luminal layer may show prominent hobnailing, and classical acinic cells may be very infrequent. In addition, this variant often shows intratumoral and intracystic hemorrhage, and phagocytosis of hemosiderin by tumor cells is sometimes a conspicuous feature. The follicular pattern (Fig. 86C) is the least common variant and consists of multiple cystic spaces of varying sizes. These are lined predominantly by cells of the intercalated

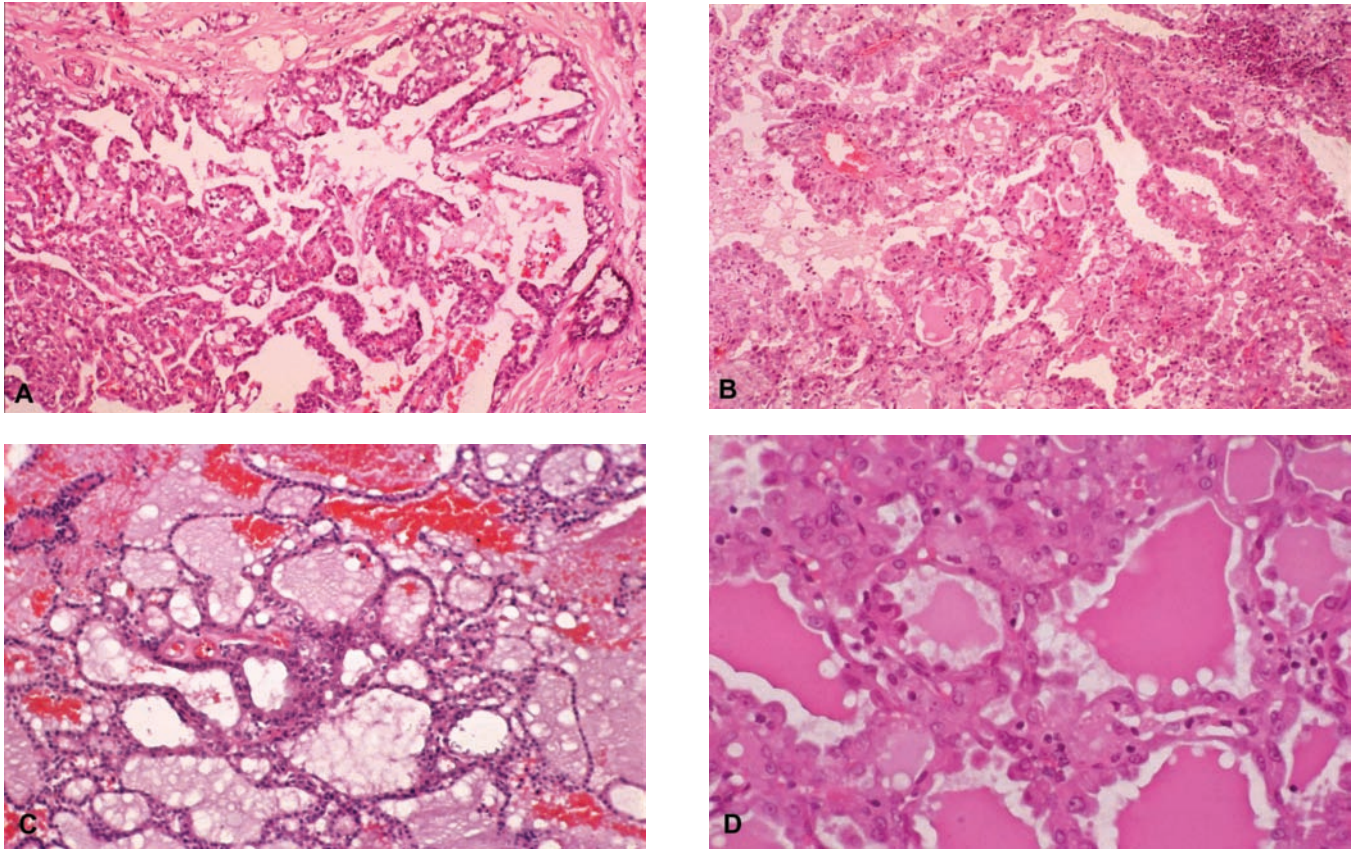


Figure 86 (A) Acinic cell carcinoma. Papillary-cystic variant consisting of basophilic cells. (B) Acinic cell carcinoma. Papillary-cystic variant consisting of nonspecific glandular and clear cells. In this variant there is characteristic luminal blebbing. (C) Acinic cell carcinoma with basophilic acinar cells forming follicles. (D) Acinic cell carcinoma with nonspecific glandular cells forming follicles containing colloid material and resembling thyroid tissue.

duct type and contain homogeneous, eosinophilic, and proteinaceous material. The intercystic areas consist predominantly of nonspecific glandular cells. The follicular variant often shows a striking similarity to follicular carcinoma of the thyroid gland (Fig. 86D). Psammoma bodies are sometimes a conspicuous feature of acinic cell carcinoma and have been described in fine-needle aspiration biopsies (Fig. 87) (28). The stroma of acinic cell carcinoma is usually scanty and composed of delicate fibrovascular tissue. Occasionally there is denser, hyalinized stroma. There may be extensive intratumoral hemorrhage, degeneration, and necrosis following fine-needle aspiration or spontaneous infarction (29). Stromal infiltration by lymphocytes is common but in some cases there is conspicuous tumor-associated lymphoid proliferation often together with germinal center formation (30). These tumors tend to be of the solid or microcystic type, have a low Ki-67 proliferation index, and are encapsulated. This variant has been termed well-differentiated acinic cell carcinoma with abundant lymphoid stroma (Fig. 88) (31). Preliminary data

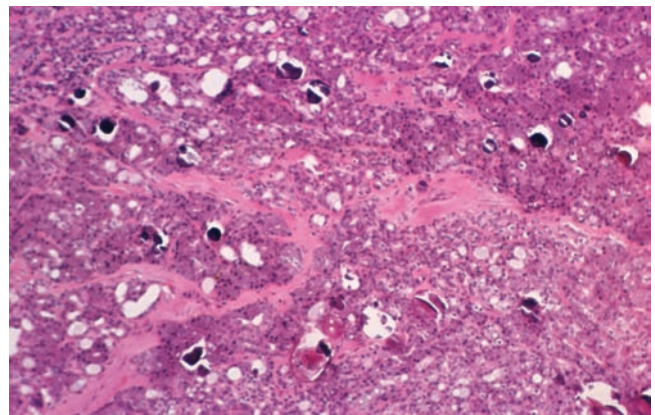


Figure 87 Acinic cell carcinoma with extensive psammoma body formation.

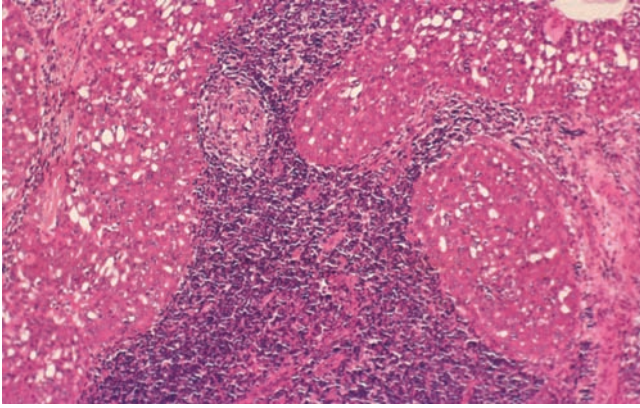


Figure 88 Well-differentiated acinic cell carcinoma with abundant lymphoid stroma.

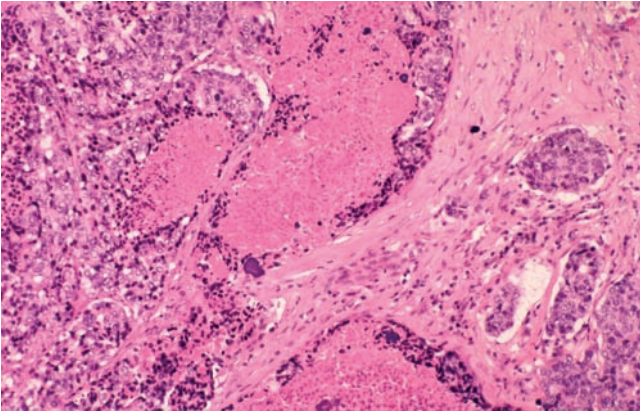


Figure 89 Area of high-grade tumor with extensive necrosis.

suggest that this subgroup has a very good prognosis. Dedifferentiated acinic cell carcinomas have also been reported (32–35). They are composed of typical acinic cell carcinoma with areas of poorly differentiated, high-grade tumor (Fig. 89); this component is usually adenocarcinoma (NOS) or undifferentiated but a carcinomatous element showing myoepithelial differentiation has been described (36). Extensive oncocytic change has rarely been reported (37).

Immunohistochemistry. The immunohistochemical profile of acinic cell carcinoma is nonspecific and is rarely of diagnostic value (38,39). Although the zymogen granules of normal salivary glands stain consistently for anti- α -amylase, those in acinic cell carcinoma show very variable reactivity (40,41). Immunoreactivity has been reported for cytokeratins, carcinoembryonic antigen, Leu M1, α 1 antichymotrypsin (39,42), vasoactive intestinal polypeptide (43), COX-2 (44), and bone morphogenic protein 6 (45). Some tumors are positive for estrogen and progesterone receptors (46), and prostate-specific antigen (47).

Although about 10% of acinic cell carcinomas are positive for S-100 protein (39), there appears to be no evidence of basal cell or myoepithelial differentiation (48,49). In a recent study, cytokeratin 14, which has been used as a myoepithelial marker, was detected in a wide range of salivary tumors but was not a feature of acinic cell carcinomas (50).

Differential diagnosis. The degree of variability can lead to considerable difficulty in diagnosis of some acinic cell carcinomas by less experienced histopathologists. Well-differentiated tumors need to be distinguished from normal salivary serous acini or sialadenitis, particularly in biopsy material and frozen sections. The lack of other structures such as striated ducts should assist recognition. Microcystic and papillary-cystic acinic cell carcinomas need to be differentiated from cystadenocarcinomas, particularly the papillary variant. The presence of characteristic zymogen granules, vacuolated cells, and intercalated ductal differentiation aids distinction. The characteristic hob-nail appearance of luminal cells and the vascularity of papillary-cystic acinic cell carcinoma are also useful distinguishing features. Microcystic variants can also be confused with mucoepidermoid carcinoma due to the mucicarmine positivity of the small cystic spaces being interpreted as mucocytes (51). However, there is a lack of other characteristic features of mucoepidermoid carcinoma such as intermediate and epidermoid cells, and close scrutiny shows an absence of typical goblet cells. When there is difficulty separating adenocarcinoma (NOS) and acinic cell carcinoma, staining for cytokeratin 7 and cytokeratin 18 may be helpful (52). Cytokeratin 7 is strongly positive in adenocarcinoma (NOS) but completely or predominantly negative in acinic cell carcinoma. In addition, cytokeratin 18 shows characteristic membranous staining in acinic cell carcinomas but there is diffuse cytoplasmic staining in adenocarcinoma (NOS). The follicular variant of acinic cell carcinoma can be mistaken for follicular thyroid carcinoma but in equivocal cases staining for thyroglobulin quickly resolves the dilemma. The differential diagnosis when significant numbers of clear cells are present is discussed in page 563. It is important that acinic cell carcinomas with a prominent lymphoid stroma are not misinterpreted as lymph node metastases.

Molecular-genetic data. There have been few cytogenetic or molecular genetic studies on acinic cell carcinomas, and some results are conflicting so that any interpretation should be circumspect. Deletion of chromosome 6q, loss of the Y chromosome, and trisomy 21 have been described, but these abnormalities are neither constant nor specific (53,54). Analysis of a single tumor has shown cytogenetic and genetic evidence of polyclonality (55). In the largest study on genetic alterations in acinic cell carcinoma, the highest incidence of loss of heterozygosity was found at 4p15-16, 6p25qter and 17p11, suggesting the presence of tumor suppressor genes (56). Twenty-one out of 24 cases showed alteration in at least one locus tested, with the most frequent involvement on chromosomes 1p and 1q and 4q, 5p and 6q. It has been shown that Rb protein is expressed in significant levels in acinic

cell carcinomas suggesting that it is not commonly mutated (57). However, phosphorylation of serine 795 resulting from cyclin D over-expression was more frequent in tumors than normal salivary gland tissue. In addition, there appeared to be no changes in p16^{INK4a} expression in the tumors compared with normal tissue. This observation correlates with those reports showing there was no loss of heterozygosity in these tumors (58).

Treatment and prognosis. There is considerable variation in the reported rates of local recurrence (8–60%) and both regional and distant metastasis (7–29%) (59). The wide range of incidence may reflect inappropriately conservative initial management in earlier cases. The average recurrence rate is about 35%, and the average rate of metastasis and disease-associated death is about 16% (2). In a meta-analysis of over 2000 cases, the 5- and 10-year survival was 82% and 68%, respectively (60). Multiple recurrences, locoregional or distant metastases, usually to lung or bone, are associated with a very poor prognosis (23,61). Tumors in the minor glands have a better outcome than those in major glands (24,62–65), and submandibular gland tumors have the worst prognosis. Histologic grading is of limited value in assessing outcome (15,59). Features associated with more clinically aggressive tumors include a high mitotic frequency, cellular pleomorphism, necrosis, perineural or vascular invasion, stromal desmoplasia, and widespread invasion (14,39,59,61,66). Attempts to devise a histopathologic grading system based on architectural characteristics, invasion, and vascular involvement have not received universal acceptance (66). One study found that a predominantly solid architecture was a strong predictor of recurrence (67). Ki-67 proliferation index may be a useful predictor of clinical behavior (68,69). DNA studies have produced conflicting results in predicting likely outcome (70–73). Dedifferentiated acinic cell carcinoma is associated with a particularly poor prognosis. Clinical staging appears to be the best indicator of clinical outcome. Large tumors (>6 cm diameter) and involvement of the deep lobe of the parotid gland (4,15,21,61) are associated with a worse outcome.

Surgical excision is the treatment of choice, and failure to excise the tumor completely in the initial operation is an indicator of poor prognosis (22). Superficial parotidectomy is the most commonly employed surgical procedure, and neck dissection is not undertaken unless there is a specific indication, as there is a low reported incidence of regional metastases. Radiotherapy appears to be of limited value (59,61).

Mucoepidermoid Carcinoma

Introduction. Mucoepidermoid carcinoma is a malignant epithelial neoplasm characterized by the proliferation of epidermoid, mucous, and intermediate type cells in various proportions (1,2). This malignancy exhibits varying degrees of differentiation and histologic grade as well as widely diverse biologic behavior.

In 1945, Stewart et al. were the first to describe this neoplasm as “mucoepidermoid tumor” (3). They divided this tumor into two varieties: “relatively favorable” (benign) and “highly unfavorable” (malignant). In 1953, Foote and Frazell reported that some patients with “relatively favorable” tumors, included in the previous citation, developed distant metastases (4). Nevertheless, the 1st edition of the *WHO Histological Classification of Salivary Gland Tumors*, published in 1972, retained the term mucoepidermoid tumor, for the reason that only minority do eventually metastasize and in only a very few does invasiveness assume a serious degree, though these tumors must be regarded as potentially malignant (5). Now, all of these tumors are considered to be malignant with the capability to recur or metastasize to regional lymph nodes or to distant viscera, regardless of their macroscopic or microscopic appearances. Thus, the 2nd and 2005 editions of the WHO classification adopted the term mucoepidermoid carcinoma (2,6). Mucoepidermoid carcinoma has been defined as “a malignant glandular epithelial neoplasm characterized by mucous, intermediate, and epidermoid cells, with columnar, clear cell and oncocytoid features (2).

Clinical features. Mucoepidermoid carcinoma is the most common malignant salivary gland tumor in both major and minor salivary gland sites, accounting for about 2% to 16% of all salivary gland tumors and 12% to 29% of all salivary gland malignancies (1,7,8). Slightly over half of the tumors arise in the major salivary glands. In the major salivary glands, the parotid gland is the most frequent site (45%), followed by 7% in the submandibular gland and 1% in the sublingual gland (1). The palate is the most frequently involved minor salivary gland site, but the buccal mucosa, upper and lower lips, retromolar region, and tongue may be affected (1,7).

Mucoepidermoid carcinoma can arise from ectopic salivary gland tissue in periparotid lymph nodes as well as in the larynx, lacrimal gland, nose, paranasal sinuses, lung, and trachea (9). Rarely, it originates in the mandible and maxilla as an intraosseous tumor, referred to as “central mucoepidermoid carcinoma” (1,10–13). The histogenesis of central mucoepidermoid carcinoma remains controversial, but one highly possible theory is that this malignancy arises from the lining epithelium of odontogenic cysts (1,10–13).

The majority of mucoepidermoid carcinoma occurs between the third and sixth decades of life with a mean patient age of about 45 years, but it may present at any age (2). Patients with palatal tumors are about 7 years younger than those with other intraoral minor salivary gland tumors (1). It is the most common salivary gland malignancy of children, and most tumors in this age group are low grade (14,15). There is a slight female predominance with a 3:2 female to male ratio (1).

Prior exposure to ionizing radiation is the most common etiologic factor associated with the development of mucoepidermoid carcinoma. Atomic bomb survivors exposed to radiation in Hiroshima and Nagasaki have suffered mucoepidermoid

carcinoma in high incidence with a relative risk of 9.3 times (16). In addition, the occurrences of mucoepidermoid carcinoma have been reported in the patients after radiation treatment for leukemia, lymphoma, brain tumor, sarcoma, retinoblastoma, or thyroid carcinoma (17).

Clinically, patients with mucoepidermoid carcinoma typically complain of a slowly growing, firm, and painless swelling, but a high-grade tumor may present as a rapidly enlarging mass accompanied by pain, fixation, otorrhea, paresthesia, facial nerve palsy, dysphagia, hemorrhage, or trismus (1). Many palatal tumors appear as fluctuant, bluish, smooth-surfaced swellings resembling mucocles.

Pathology. Macroscopically, mucoepidermoid carcinoma typically manifests as a circumscribed but unencapsulated or incompletely capsulated, firm mass. High-grade tumors are poorly circumscribed and have infiltrative borders, often with fixation to the adjacent tissue. The cut surface commonly has conspicuous cystic structures accompanied by grayish white to tan solid areas (Fig. 90). Cystic spaces may contain brownish and mucinous material. Hemorrhage or necrosis is frequently present in high-grade tumors, and these tumors tend to be solid. In the AFIP series, the tumor size ranges from less than 1 cm to over 12 cm in the major salivary glands and as large as 5 cm in the minor salivary glands (1).

Microscopically, mucoepidermoid carcinomas are characteristically composed of varying proportions of three basic cell types: epidermoid (squamous), mucous (mucus-producing), and intermediate (Fig. 91). Furthermore, columnar cells, clear cells, and oncocytic cells may also be components of these tumors. Epidermoid cells are polygonal in shape with ovoid to elongated, vesicular nuclei, and abundant eosinophilic cytoplasm. Individual cell keratinization and keratin pearl formation are only rarely seen in

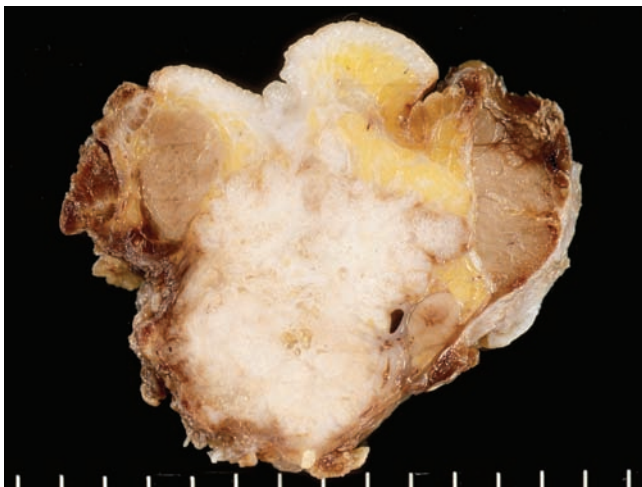


Figure 90 Mucoepidermoid carcinoma. Cut surface of the intermediate-grade tumor shows gray-white, solid mass accompanied by multiple small cystic structures and infiltrative borders.

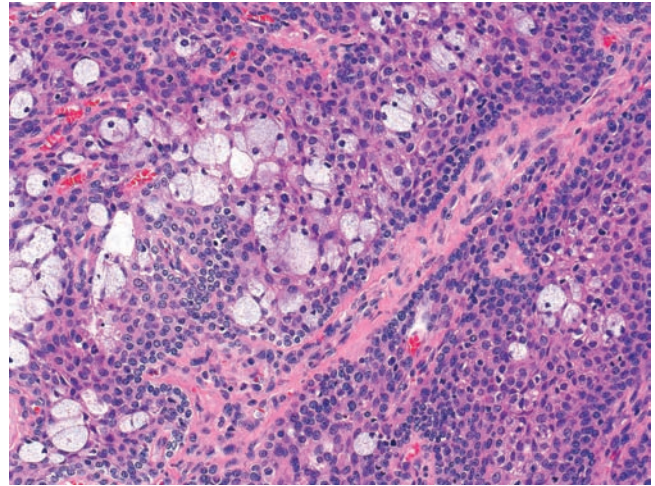


Figure 91 Mucoepidermoid carcinoma. Tumor is composed of a mixture of three cell types: epidermoid, mucous (mucus-producing), and intermediate.

mucoepidermoid carcinoma and if present, usually occur in inflamed portions. Epidermoid cells are negative for mucicarmin but may show faint positivity for PAS stain. Mucous cells are large and have pale to slightly basophilic, fine cytoplasm with positive reactions to PAS, Alcian blue, and mucicarmin stains. Their nuclei are compressed and located at the periphery of the cell. Intermediate cells are ovoid in shape with scanty cytoplasm and the size ranges from small, resembling basal cells, to about three times larger than lymphocytes. These cells exhibit a small, centrally located, darkly stained nucleus and pale eosinophilic cytoplasm, which is negative for mucin stains. Larger intermediate cells transitionally merge into epidermoid or mucous cells.

Columnar cells superficially mimic duct luminal cells of the excretory salivary duct and can transform into mucous cells. Clear cells are large and polygonal in shape with sharply demarcated borders that contain largely glycogen and occasionally mucin as well. These cells are present in many mucoepidermoid carcinomas and uncommonly are a dominant component of the tumor (clear cell variant) (Fig. 92A) (18,19). Oncocytic differentiation may be a focal feature of some mucoepidermoid carcinomas, but it is rarely extensive “oncocytic variant,” with only 14 such cases reported (Fig. 92B) (20,21). The majority of oncocytic mucoepidermoid carcinoma are low-grade tumors and should not be misdiagnosed as oncocytoma. In addition, a few cases of intraoral mucoepidermoid carcinoma have been associated with melanin pigmentation (22).

Mucoepidermoid carcinoma is characterized by a variety of tumor-cell types arranged in a combination of cystic or ductal structures and solid nests in various proportions. The cystic structures are lined by mucous, intermediate, epidermoid, or columnar cells.

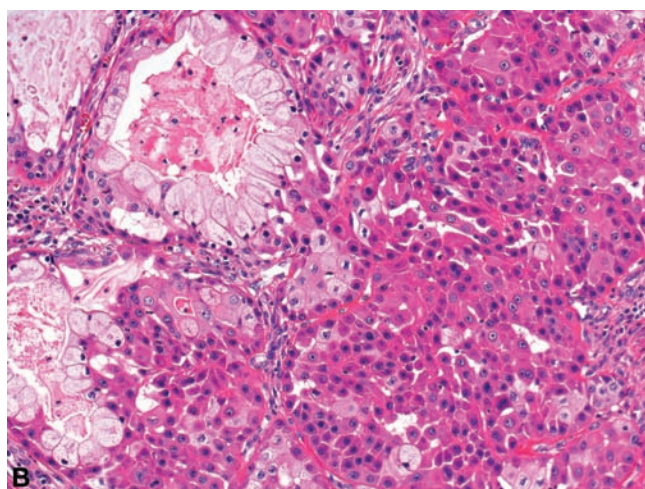
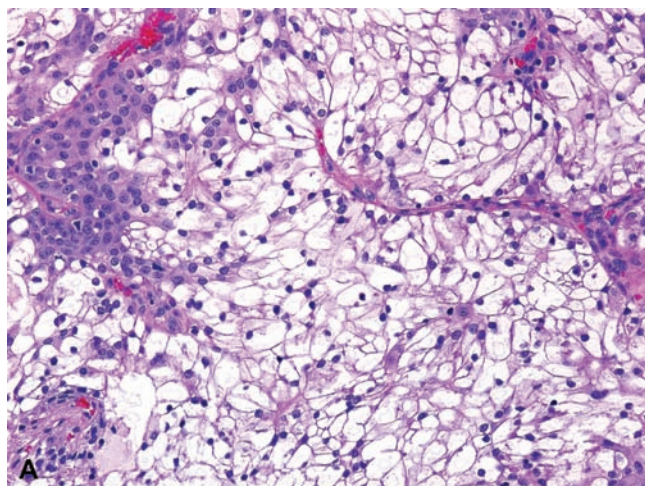


Figure 92 Mucoepidermoid carcinoma. (A) Clear cell variant. (B) Oncocytic variant.

Cystic spaces contain mucinous material, which occasionally leaks into the stromal tissue, forming mucin pools. The ductal structures are formed by clear and columnar cells. The solid nests are composed mainly of intermediate cells admixed with epidermoid, mucous, clear, and uncommonly oncocytic cells. The fibrous stroma is usually abundant and sometimes hyalinized (Fig. 93A). Hyalinization may be pronounced and rarely is accompanied by dense eosinophilic cell infiltration (sclerosing mucoepidermoid carcinoma with eosinophilia) (23–25). Extensive secondary lymphoid cell infiltration, referred to as tumor-associated lymphoid proliferation (26), is commonly present (Fig. 93B); the feature may be confused with metastasis to or origin from ectopic salivary gland tissue in intraparotid lymph nodes.

The histopathologic features of mucoepidermoid carcinoma are complex and largely depend on the histologic grade; these tumors are generally classified

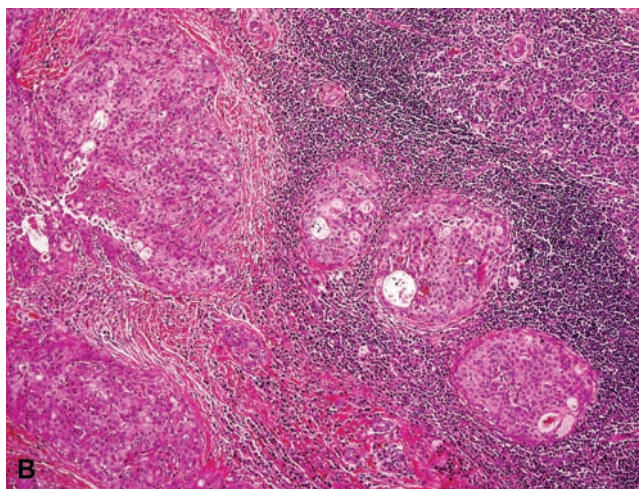
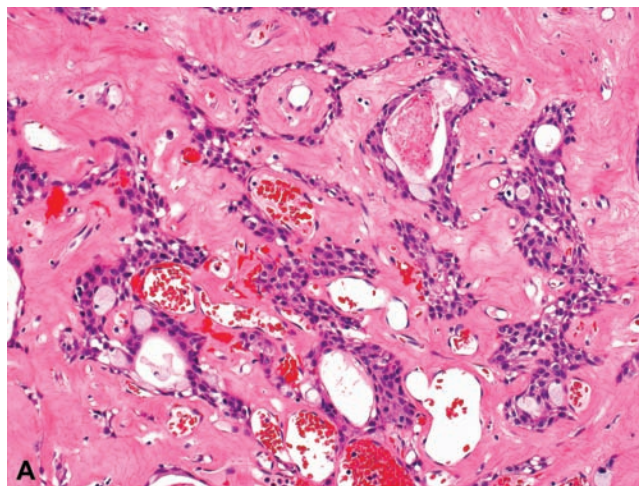


Figure 93 Mucoepidermoid carcinoma. (A) Abundant hyalinized stroma is evident. (B) Extensive secondary lymphoid cell infiltration, referred to as tumor-associated lymphoid proliferation.

into low grade, intermediate grade, or high grade. Low- and intermediate-grade mucoepidermoid carcinomas tend to have a more favorable outcome than high-grade tumors, which have a greater tendency to recur and metastasize.

Many investigators have tried to define histologic features that have prognostic significance and proposed various grading schemes (3,4,27–33). In the literature, the histopathologic grading criteria of mucoepidermoid carcinoma remain controversial. However, the AFIP scoring system offers good correlation with clinical outcome and high reproducibility (1,29,31,34) (Table 6). The grading is based on a scoring system of five histologic features: intracystic component <20% (+2), neural invasion (+2), necrosis (+3), 4 or more mitotic figures per high-power fields (+3), and anaplasia (+4); and based on the total score a case is categorized as low grade (score 0–4), intermediate grade (score 5–6), or high grade (score > 6)

Table 6 Histologic Grading System (Armed Forces Institute of Pathology)

Parameter	Point value	
Intracystic component <20%	+2	
Neural invasion present	+2	
Necrosis present	+3	
Four or more mitoses per 10 HPFs	+3	
Anaplasia	+4	
Grade	Total score	Death of disease ^a
Low grade	0–4	3.3%
Intermediate grade	5–6	9.7%
High grade	7 or more	46.3%

^aFive-year mortality rate.

Abbreviation: HPFs, high-power fields.

Source: From Ref. 31.

(Table 6). The cellular anaplasia is represented by cellular and nuclear pleomorphism, increased nuclear-cytoplasmic ratio, prominent or multiple nucleoli, and hyperchromasia. This system is applicable to the parotid gland and intraoral minor salivary gland tumors, but it does not predict outcome of submandibular tumors, which have a significant metastatic potential irrespective of histologic grade (29,31). On the other hand, Brandwein et al. noted that the AFIP scoring system tends to downgrade mucoepidermoid carcinomas (32) (Table 7). Their modified grading system adds three additional parameters (invasion in the form of small nests or islands, lymphovascular invasion, and bony invasion).

Low-grade tumors are characteristically composed of multiple cystic structures of variable sizes that are lined predominantly by mucous cells (Fig. 94). Some cysts may have focal papillary projections of lining epithelial cells. Usually, mucous cells are more common than intermediate- and high-grade tumors. Solid nests are a minor component and are composed mainly of intermediate cells. Squamous cell differentiation and clear cell change may be present, at least focally. In low-grade tumors, cellular or nuclear pleomorphism is absent, and mitotic figures are rare. Tumor borders are generally well circumscribed and minimally invasive. However, a case of dedifferentiation to anaplastic, undifferentiated carcinoma from histologically low-grade mucoepidermoid carcinoma has been reported (35).

Intermediate-grade tumors have less tendency to form cystic structures and contain smaller cystic spaces (Fig. 95). In most cases, cyst-lining cells are mainly columnar cells with occasional mucous cells. Solid sheets or nests, consisting of intermediate cells as well as epidermoid cells, become a conspicuous component in intermediate-grade tumors compared with low-grade tumors. Intermediate-grade tumors show an invasive growth pattern, at least focally. Mild to moderate cellular pleomorphism and a few mitotic figures may be seen.

High-grade tumors manifest as predominantly solid nests with scanty cystic structures (Fig. 96). They have markedly infiltrative borders. These

Table 7 Histologic Grading System Proposed by Brandwein et al.

	Characteristic features	Defining features
Grade I	– Prominent goblet cell component – Cyst formation and intermediate cells may be prominent – Circumscribed growth pattern	– Lack of grade III defining features – Lack of aggressive invasion pattern
Grade II	– Intermediate cells predominate over mucinous cells – Mostly solid tumor – Squamous cells may be seen	– Aggressive invasion pattern – Lack of grade III defining features
Grade III	– Squamous cells predominate – Intermediate and mucinous cells must also be present – Mostly solid	– Necrosis, perineural spread, vascular invasion, bony invasion, >4 mitosis/10 HPFs, high-grade nuclear pleomorphism
Features		Points
Intracystic component < 25%		2
Tumor front invades in small nests and islands		2
Pronounced nuclear atypia		2
Lymphatic or vascular invasion		3
Bony invasion		3
> 4 mitoses/10 HPFs		3
Perineural spread		3
Necrosis		3
Grade	Total points	Death of disease ^a
I	0	0%
II	2 or 3	5%
III	4 or more	63%

^aMortality rate at 36 months.

Abbreviation: HPFs, high-power fields.

Source: From Ref. 32.

tumors are composed primarily of epidermoid cells and a small proportion of intermediate cells, which usually have marked cellular pleomorphism and high mitotic activity. Necrosis may be present, and perineural and lymphovascular invasion is common. Some areas of high-grade mucoepidermoid carcinoma may resemble nonkeratinizing squamous cell carcinoma. Since mucous cells are few and are scattered within the tumor cell nests, mucin stains are often required to identify them. Foci of low-grade mucoepidermoid carcinoma are rarely present within high-grade tumors. In addition, a case of high-grade mucoepidermoid carcinoma with a spindle cell sarcomatoid component has been reported (36).

A few examples of mucoepidermoid carcinoma arising in or associated with Warthin's tumor (37), pleomorphic adenoma (38), salivary duct cyst (39), and odontogenic cyst (10) have been reported.

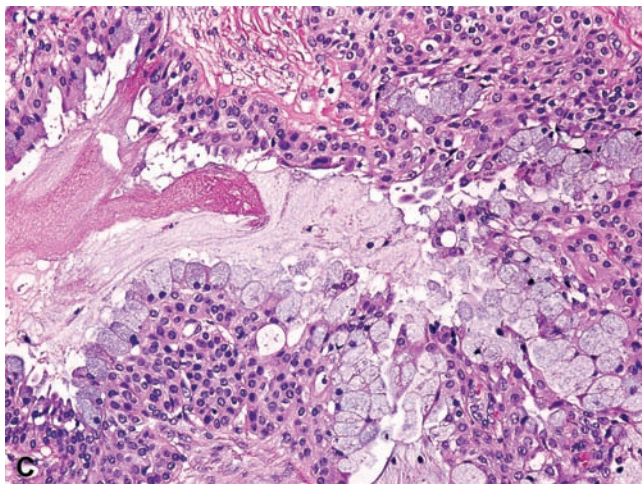
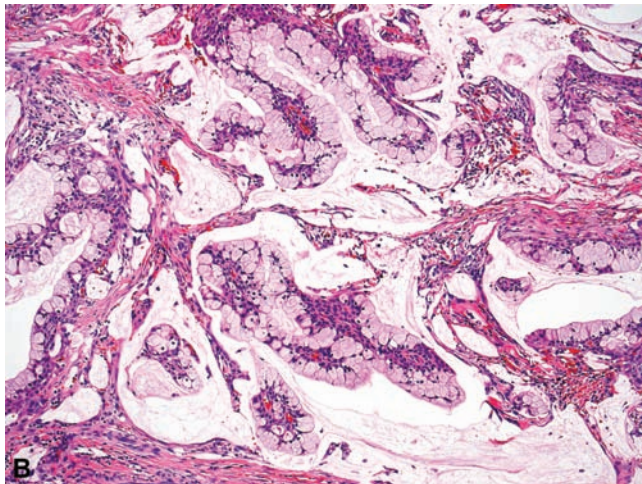
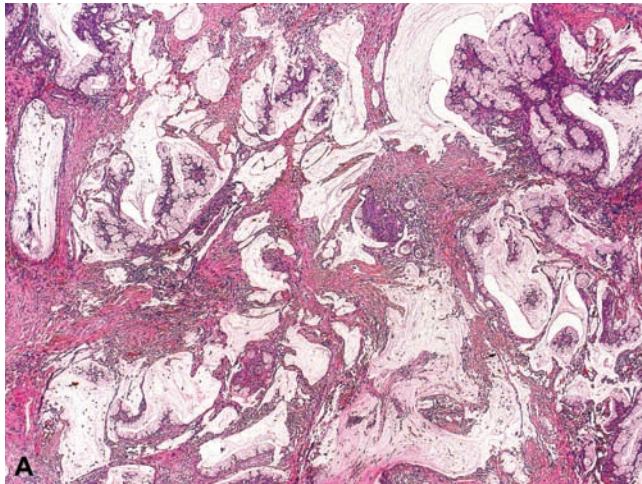


Figure 94 Low-grade mucoepidermoid carcinoma. (A) Multiple cystic structures of variable sizes with focal papillary projections. (B) The cyst linings and papillary projections are mainly composed of mucous cells. (C) High-magnification view shows mucous, intermediate, and columnar cells with minimal atypia.

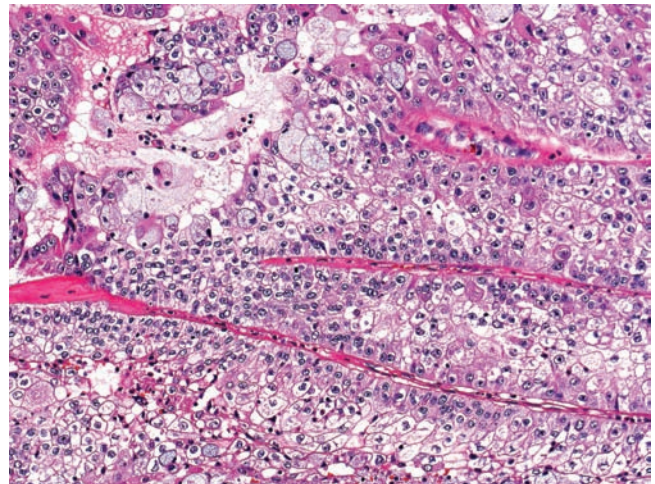


Figure 95 Intermediate-grade mucoepidermoid carcinoma. Solid nests with focal cystic structures consisting of intermediate cells as well as epidermoid cells and a few mucous cells. Note mild to moderate cellular pleomorphism.

Immunohistochemistry. Tumor cells are positive for pan-cytokeratin and are variably immunoreactive for epithelial membrane antigen, carcinoembryonic antigen, and S-100 protein. Intermediate, epidermoid, and clear cells may be positive for p63 but completely negative for smooth muscle actin and calponin (40).

Molecular-Genetic data. A chromosomal translocation, $t(11;19)(q21;p13)$, has been found in mucoepidermoid carcinoma as a sole-specific cytogenetic alteration (41). Molecular analysis demonstrates that the fusion transcript, resulting in the binding *MECT1* at 19p13 with *MAML2* at 11q21, is detected in 38% to 81% of mucoepidermoid carcinoma cases (42–44). The *MECT1*-*MAML2* fusion transcript acts as a coactivator for Notch receptor transcriptional activation and signaling (45). This translocation is frequently associated with a low-grade histology, and the presence of this transcript appears as an independent prognostic factor (42,43). The fusion transcript has been detected using reverse transcription-polymerase chain reaction assay also in some cases of Warthin's tumor but not in any cases of adenoid cystic carcinoma, basaloid carcinoma, salivary duct carcinoma, and adenocarcinomas (NOS) (44). Recently, fusion between *EWSR1* and *POU5F1* has also been reported in a single case of high-grade mucoepidermoid carcinoma with the translocation $t(6;22)(p21;q12)$ (46). The fusion transcript is expected to be useful in the development of novel molecular therapeutic strategies for patients with mucoepidermoid carcinoma (47).

Differential diagnosis. The main differential diagnoses include necrotizing sialometaplasia, pleomorphic adenoma, cystadenoma, and cystadenocarcinoma for low-grade mucoepidermoid carcinoma, squamous cell carcinoma and adenosquamous carcinoma for high-grade mucoepidermoid carcinoma, and

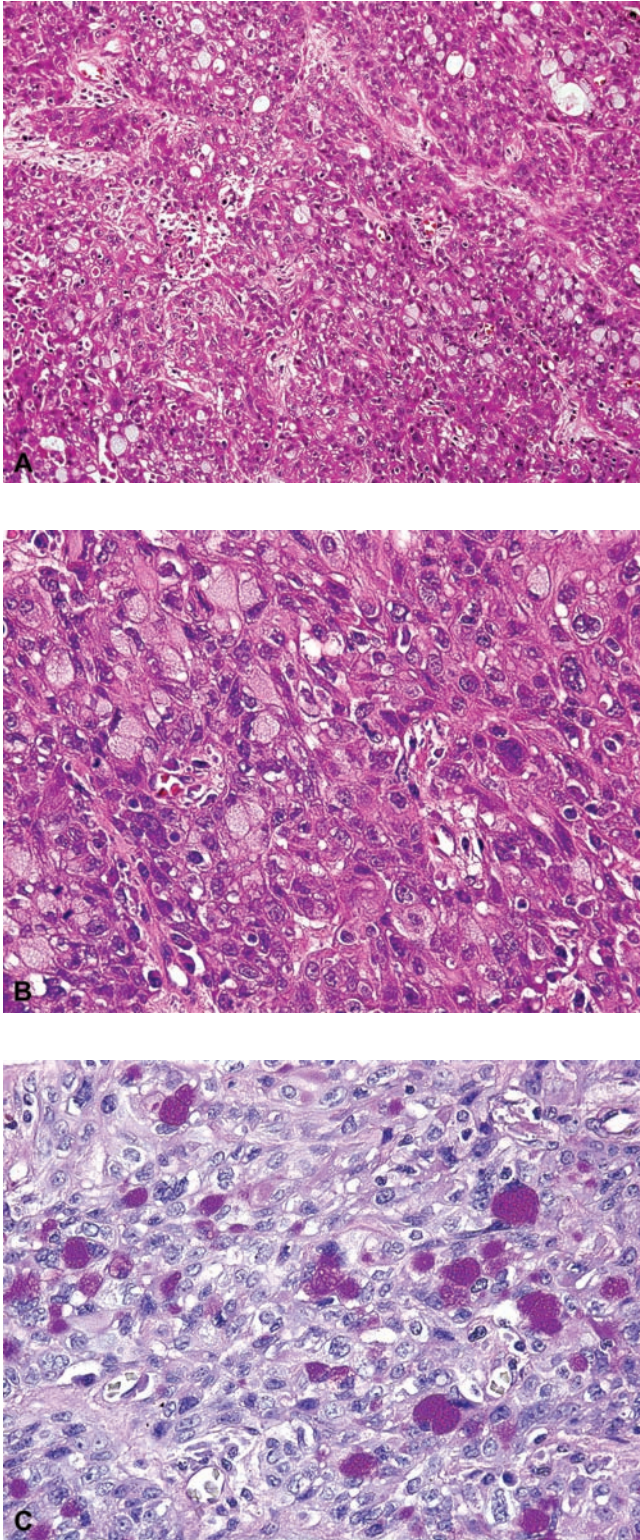


Figure 96 High-grade mucoepidermoid carcinoma. (A) Solid nests accompanied by focal necrotic area and scanty cystic structures. (B) Tumor is composed primarily of markedly pleomorphic epidermoid cells and a small proportion of mucous cells. (C) Periodic acid–Schiff (PAS) stain showing scattered positive mucous cells in the solid nests.

clear cell tumors for the clear cell variant of mucoepidermoid carcinoma (1,33).

Necrotizing sialometaplasia exhibits squamous metaplasia of ducts and acini with adjacent lobules containing mucus or necrotic debris. While these features can be confused with mucoepidermoid carcinoma, in necrotizing sialometaplasia, the lobular architecture is maintained, and the cystic structures and intermediate cells of mucoepidermoid carcinoma are absent. In addition, identification of myoepithelial cells demonstrated by calponin and/or smooth muscle actin in necrotizing sialometaplasia may help to distinguish it from mucoepidermoid carcinoma (40).

The epithelioid type of neoplastic myoepithelial cells seen in pleomorphic adenoma may mimic intermediate cells in mucoepidermoid carcinoma. The presence of myxochondroid areas, plasmacytoid-type myoepithelial cells, and small, well-defined ductal structures is diagnostic for pleomorphic adenoma but not for mucoepidermoid carcinoma. Cystadenoma and cystadenocarcinoma and low-grade mucoepidermoid carcinoma share conspicuous multicystic and papillary structures. Cystadenoma and cystadenocarcinoma lack solid nests consisting of a mixture of epidermoid, mucous, and intermediate cells characteristic of low-grade mucoepidermoid carcinoma.

The distinction between high-grade mucoepidermoid carcinoma with extensive squamous differentiation and squamous cell carcinoma is based on the presence or absence of mucous cells revealed by mucin stains. Also, marked intracellular keratinization and keratin pearl formation are much more commonly seen in squamous cell carcinoma than in mucoepidermoid carcinoma. Positive immunostaining for MUC1 and MUC5AC in high-grade mucoepidermoid carcinoma can be helpful in distinction from squamous cell carcinoma (48,49). In addition, most mucoepidermoid carcinomas stain positively for cytokeratin 7 and negatively for cytokeratin 20, while squamous cell carcinomas generally stain negatively for these cytokeratin subtypes (50). Adenosquamous carcinoma is composed of two separate carcinomatous components showing squamous and glandular differentiation. By contrast, the squamous and mucinous glandular components of mucoepidermoid carcinoma are usually markedly admixed with each other in the same tumor nests.

The clear cell variant of mucoepidermoid carcinoma should be distinguished from various types of salivary gland tumors composed predominantly of clear cells, such as sebaceous carcinoma, clear cell adenocarcinomas (NOS), epithelial-myoepithelial carcinoma, oncocytoma, acinic cell carcinoma, and metastatic renal cell carcinoma (see the section “Clear Cell Carcinoma, NOS”) (19,51). Only mucoepidermoid carcinoma displays both epidermoid and mucous cell differentiation.

Treatment and prognosis. The biologic behavior of mucoepidermoid carcinoma varies depending on the clinical stage, the histologic grade, tumor location, and the adequacy of treatment, but the majority is low-grade and the prognosis is generally favorable. Overall, 75% of patients with mucoepidermoid carcinoma are tumor free after the initial treatment, 9%

have local recurrence only, 5% develop metastasis and survive, and 11% die of disease (31).

The clinical stage appears to be the most significant prognostic indicator of mucoepidermoid carcinoma. Five-year survival rates of the patients have been reported to be 97% to 100%, 70% to 83%, and 20% to 37% for stage I, II, and III cases, respectively (7,33,52). Histologic grade also closely correlates with patient outcome. However, the clinical stage is a stronger prognostic indicator than the histologic grade.

There are some differences in survival rate among the histologic grades reported in the literature, because of the variable histologic grading criteria used (3,4,27–32) (Tables 6 and 7). Low-grade tumors rarely recur or metastasize. According to the AFIP, 5% of major gland and 2.5% of minor gland low-grade mucoepidermoid carcinomas metastasized to regional lymph nodes or resulted in death of the patient (1). Most investigators have indicated that the five-year survival rate is over 92% in the low-grade tumor group. Intermediate-grade tumors have a slightly higher tendency of recurrence and metastasis than low-grade tumor. Healey et al. reported that recurrence rate following surgery of intermediate tumor is 20% compared with 6% for low-grade tumor (27). The five-year survival rate of intermediate-grade mucoepidermoid carcinoma ranges from 62% to 92%.

High-grade tumors are much more likely to have recurrence and metastases than low- and intermediate-grade tumors. The recurrence rate has been reported as 59% in high-grade tumors (31). Common sites for distant metastasis include the lungs, bones, liver, and brain. Distant metastases imply a poor prognosis; patients with minor and major salivary gland tumors with distant metastases survive 2.3 and 2.6 years on average, respectively (1). The five-year survival rate of high-grade mucoepidermoid carcinoma is up to 53%. Regarding the tumor location, submandibular gland tumors metastasize to the regional lymph nodes more frequently than other major and minor salivary gland tumors (7). The margin status of the initial excision closely correlates with the recurrence rate, regardless of tumor grade (27).

Many investigators have attempted to correlate nuclear DNA content and immunohistochemical markers of salivary gland mucoepidermoid carcinoma with prognosis. DNA ploidy pattern analysis has demonstrated that aneuploid tumors have a poorer clinical outcome than diploid tumors (52). Immunohistochemical prognostic factors include expression of Ki-67 (53–56), HER-2/*neu* (55), p53 (56), p27 (54), bcl-2 (57), caveolin-1 (58), β -catenin (59), and certain types of mucins (48,49). A Ki-67 labeling index higher than 10% is associated with high histologic grade, increasing rate of recurrence and metastasis, and decreasing survival rates in patients with mucoepidermoid carcinoma (53). Over-expression of HER-2/*neu* and p53 correlates with poor prognosis (55,56); conversely, high expression for p27 and bcl-2 is associated with a favorable outcome (54,57). Downregulation of caveolin-1, which has been proposed as a candidate tumor suppressor, is identified as a negative prognostic factor (58). Nuclear/cytoplasmic accumulation of

β -catenin is correlated with adverse outcome (59). High expression of MUC1 is related to high histologic grades, high recurrence and metastasis rates, and a shorter disease-free interval (48,49). On the other hand, high MUC4 expression is associated with low-grade tumors, lower recurrence rates, and a longer disease-free interval (49).

Complete surgical excision is the treatment of choice for mucoepidermoid carcinoma. Adequate excision is important in all grades of tumor, with much higher recurrence rates reported with positive surgical margins (27). Radiation therapy should be added in high-grade tumors and for patients with questionable or positive surgical margins or for those with positive lymph nodes. For the patients with positive surgical margins, postoperative radiotherapy may improve local control. Neck dissection is indicated when there is clinical evidence of regional metastasis, high clinical stage, high histologic grade, or proximity of tumor to regional lymph nodes.

Adenoid Cystic Carcinoma

Introduction. Adenoid cystic carcinoma is defined as “a basaloid tumor consisting of epithelial and myoepithelial cells in variable morphologic configurations, including tubular, cribriform, and solid patterns” (1). Synonyms include cylindroma, adenocystic carcinoma, adenoeplithelioma, and basaloma.

Clinical features. Adenoid cystic carcinoma accounted for 4.4% of all salivary gland tumors and 11.8% of malignant salivary neoplasms in the largest reported series (2). It affects a wide age range (9–103 years) with a peak incidence in the fifth to seventh decades, but it is very rare in children (3,4). There is a slight female preponderance in most large series, particularly in the submandibular gland (5–10). In a combined series of adenoid cystic carcinoma of the upper aerodigestive tract where the site was recorded, 42% involved the major glands and 58% the minor glands (2,11–15). The most common sites were the parotid (21%), palate (17%), and submandibular gland (13%). The tumor is rare in the sublingual gland (16). The palate accounts for nearly half of the cases in the glands of the mouth and the upper aerodigestive tract (17), and the sinonasal tract is the next most common site (18). Rare central (intraosseous) cases have been reported, the large majority involving the body and angle of mandible (19). Adenoid cystic carcinomas have been reported in wide range of other anatomical sites including the lacrimal gland (20), ceruminous glands of the external ear (21), esophagus (22), trachea (23), bronchus (24), peripheral lung (25), breast (26), skin (27), uterine cervix (28), ovary (29), Bartholin gland (30), and prostate (31).

Tumors usually present as a slow growing but widely infiltrative mass of long duration, and they can be mobile or fixed. They may be tender or painful, and cranial nerve lesions, particularly facial nerve palsy, can be the presenting feature (9,20). Patients with tumors involving the deep lobe of the parotid gland can present with trismus. It is common for tumors of

minor glands to show ulceration of the overlying mucosa. Occasionally, distant metastases are the presenting feature (32).

Pathology. Macroscopically adenoid cystic carcinoma typically forms a solid, light gray to tan colored mass. It may appear circumscribed, particularly in smaller tumors, but is rarely encapsulated. Cytologically, the tumor is composed of luminal ductal cells and abluminal, modified myoepithelial cells. The latter predominate and have indistinct cell borders and frequently sparse, amphophilic, or clear cytoplasm. The nuclei are uniform in size, basophilic, and may be round or angular (peg shaped). The ductal cells surround small and sometimes indistinct lumina; they are cuboidal and have more abundant, eosinophilic cytoplasm, and round, uniform nuclei that may contain small nucleoli. There are three main morphologic patterns: cribriform (cylindromatous), tubular, and solid in that order of frequency. A mixture of these patterns may be seen. The cribriform variant consists of islands of modified myoepithelial cells containing rounded, pseudocystic areas forming a characteristic "Swiss cheese" appearance (Fig. 97). The pseudocysts are basophilic and mucoid or consist of hyaline, eosinophilic material (Fig. 98). They are composed of glycosaminoglycans and reduplicated basement membrane material. Foci of ductal cells are present within the myoepithelial areas but may require careful examination to detect. The tubular variant is double layered and has conspicuous ductal differentiation (Fig. 99A). There is an inner layer of eosinophilic, duct-lining cells, and the abluminal myoepithelial cells may show clear cytoplasm and irregular, angular nuclei or be morphologically similar to the luminal layer (Fig. 99B). Occasionally, foci of squamous (Fig. 99C) (33), sebaceous (34), or oncocytic metaplasia (Fig. 99D) are present. The least common solid variant consists of islands or sheets of basaloid cells with larger and less angular nuclei (Fig. 100A). Duct-lining cells may be few (Fig. 100B) and inconspicuous, and comedonecrosis is common (Fig. 100C). Mitoses are sparse in the

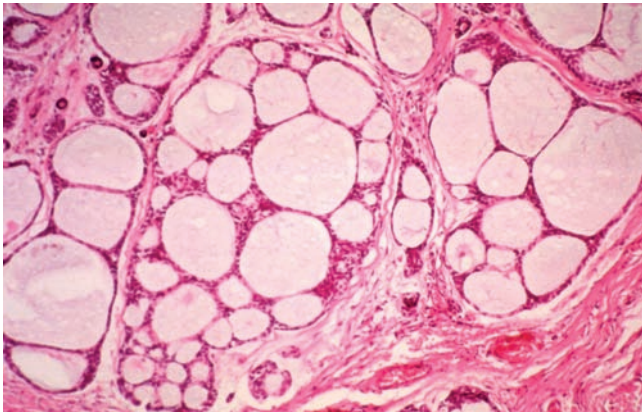


Figure 97 Adenoid cystic carcinoma showing characteristic cribriform (cylindromatous) pattern.

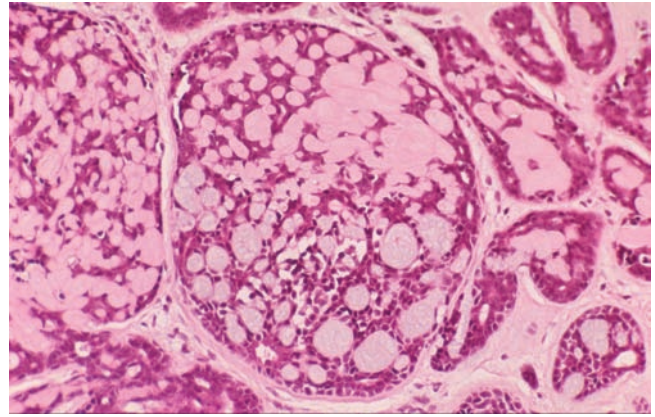


Figure 98 Adenoid cystic carcinoma showing prominent hyalinization of the stromal component.

cribriform and tubular patterns but may be frequent, often together with extensive apoptosis, in the solid type. Rare but clinically aggressive adenoid cystic carcinomas showing high-grade transformation (dedifferentiated variant) are characterized histologically by the combination of a conventional adenoid cystic carcinoma and a high-grade carcinoma (35–39). In addition, adenoid cystic carcinoma may form part of a hybrid tumor, most commonly in association with salivary duct carcinoma or epithelial-myoepithelial carcinoma (40). The stroma of adenoid cystic carcinoma is usually fibrous and may contain abundant elastic tissue (41,42). Some cases where hyalinization is so abundant that tumor cells are attenuated into strands have been reported as a sclerosing variant (Fig. 100D) (43). Perineural or intraneural invasion is common and frequently conspicuous, and the tumor can extend along nerves and their branches over a wide area (Fig. 101A). The tumor may invade bone extensively before there is any radiologic evidence bone destruction (Fig. 101B). Lymph node involvement is uncommon (~5% of cases) and is usually due to contiguous spread rather than lymphatic permeation or embolization (Fig. 101C) (44).

Immunohistochemistry. The pseudocysts are positive for PAS and Alcian blue and contain basement membrane components such as type IV collagen, heparin sulfate proteoglycan, and laminin isoforms (45,46). The epithelial cells, particularly in areas of ductal differentiation, are positive for low-molecular weight keratins, carcinoembryonic antigen, and epithelial membrane antigen (47). Duct-lining cells are also positive for c-kit (CD117) (48–50), and the myoepithelial cells are variably positive for a variety of markers including S-100 protein, calponin, smooth muscle actin, smooth muscle myosin heavy chain, maspin, metallothionein, and p63 (Fig. 101D) (47,51–53). Expression of S-100 protein, glial fibrillary acidic protein (54), and neural cell adhesion molecule (55) have been correlated with the presence of perineural invasion. High expression of both *p53* and *bcl-2* has

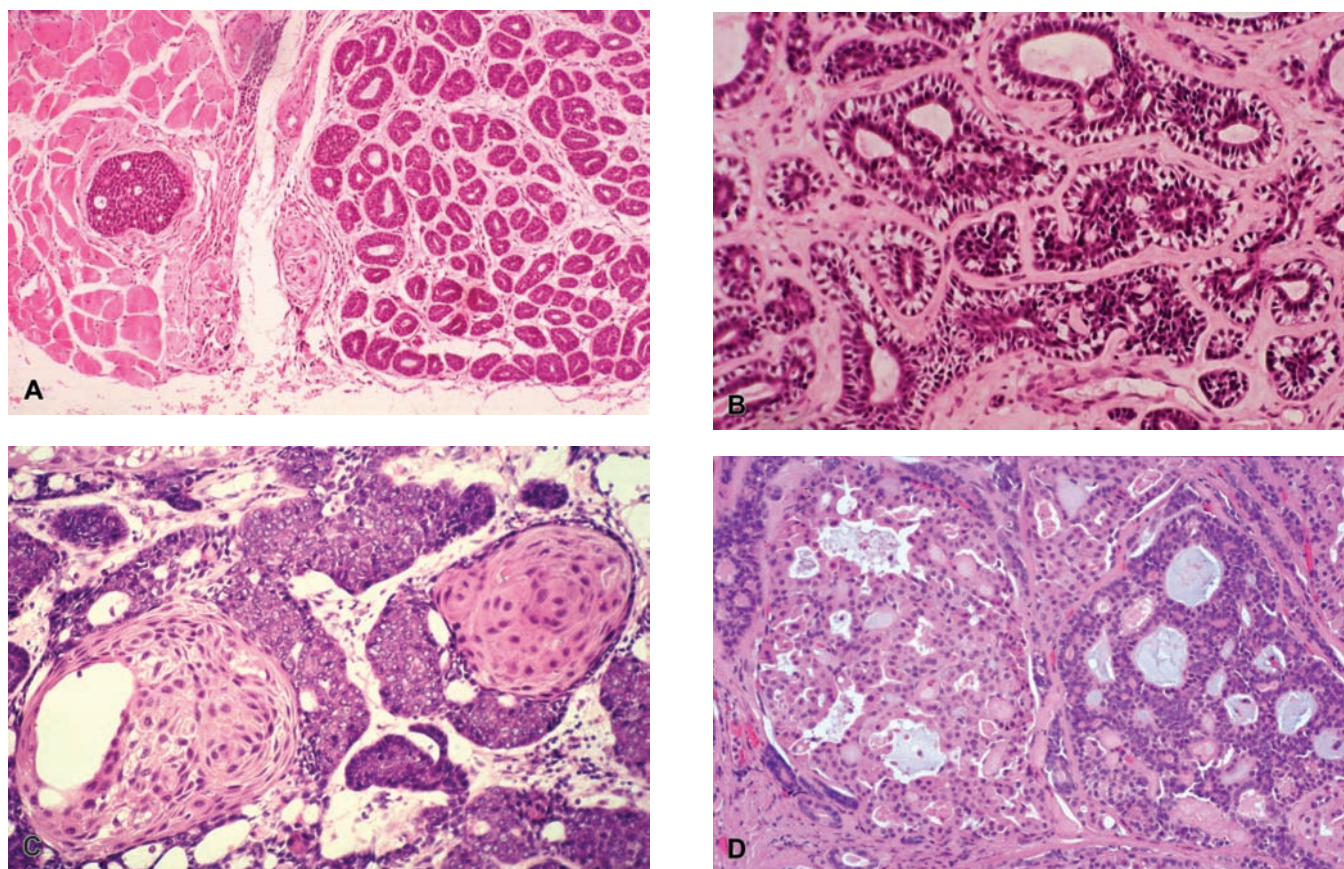


Figure 99 (A) Adenoid cystic carcinoma. Tubular variant showing morphologically similar luminal and abluminal cells. (B) Adenoid cystic carcinoma. Tubular variant showing morphologically clear abluminal cells. (C) Adenoid cystic carcinoma showing squamous metaplasia. (D) Adenoid cystic carcinoma showing oncocytic metaplasia.

been reported, but there is no consistent relationship between these observations and the histologic tumor types, clinical stage or survival (56–58). CD43, a sialoglycoprotein that is typically expressed by hemopoietic cells, has been shown to be differentially and selectively expressed in adenoid cystic carcinoma (59,60).

Molecular-genetic data. Alterations in chromosomes 6q, 9p, and 17p12-13 are the most frequent cytogenetic alterations reported (61,62). t(6;9)(q21-24;p13-23) appears to be a nonrandom, primary aberration (63). There are frequent losses at 12q, 6q23-qter, 13q21-q22, and 19q regions (64). A high frequency of loss of heterozygosity at 6q23-25 has been reported and, although not specific for adenoid cystic carcinoma, this has been correlated with both tumor grade and behavior (65,66). Over half of cases show genomic deletions of chromosome 6 (67), and candidate suppressor genes have also been mapped to chromosome 12 (68). Hypermethylation of the promoter region of the *p16* gene was found in 4/22 of adenoid cystic carcinoma and was associated with higher histologic grades of malignancy (69). In addition, promoter methylation of *p16^{INK4a}*, *RASSF1A*, and *DAPK* has been reported, and there was a high frequency of

RASSF1A promoter methylation in high-grade tumors (70). Mutations of *p53* are relatively uncommon (71,72). Alterations in *p53* and *RB* genes have been reported and correlated with behavior (73). *P53* mutation, loss of expression of *RB*, and overexpression of both *Her2/neu* and cyclin D1 have been reported in adenoid cystic carcinomas showing high-grade transformation (37,38). Frequent and plural methylation of the cyclin-dependent kinase inhibitor genes promoter regions has recently been reported (74). Microarrays and comparative genomic hybridization have been used to identify candidate genes for adenoid cystic carcinoma (75).

Differential diagnosis. It is particularly important to distinguish adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma in tumors from minor salivary glands. Polymorphous low-grade adenocarcinoma consists of a uniform cell population with cytologically bland, round or oval and vesicular nuclei and pale, eosinophilic cytoplasm, whereas cells in adenoid cystic carcinoma often have clear cytoplasm and angular, hyperchromatic nuclei and may show mitotic activity (76,77). The Ki-67 proliferative index is reported to be nearly 10× higher in adenoid

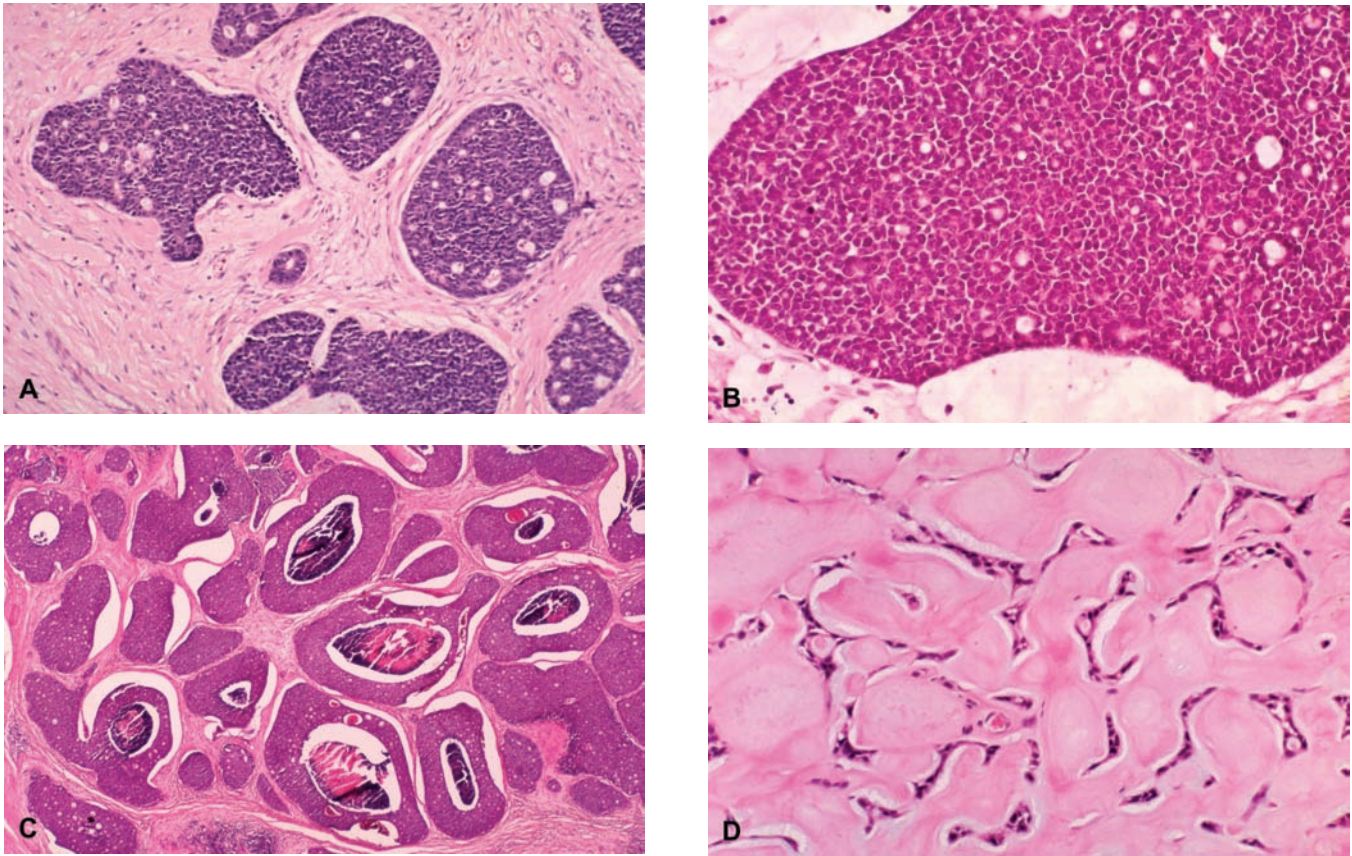


Figure 100 (A) Adenoid cystic carcinoma. Solid variant. (B) Adenoid cystic carcinoma. Solid variant higher power showing scattered duct-like structures within the tumor sheet. (C) Adenoid cystic carcinoma. Solid variant showing extensive comedo necrosis. (D) Adenoid cystic carcinoma showing extensive stromal hyalinization attenuated the tumor into thin strands.

cystic carcinoma than polymorphous low-grade adenocarcinoma with no overlap zone (78). Smooth muscle markers of myoepithelial differentiation are positive in adenoid cystic carcinoma but negative in polymorphous low-grade adenocarcinoma. In a hierarchical cluster analysis of myoepithelial/basal cell markers, the diffuse expression of smooth muscle actin was the most reliable marker in support of a diagnosis of adenoid cystic carcinoma (53). In addition, polymorphous low-grade adenocarcinoma shows a much wider spectrum of histomorphologic differentiation. Even when cribriform areas are present in polymorphous low-grade adenocarcinoma, they are typically focal, and adenoid cystic carcinoma does not show papillary differentiation or the single cord arrangement of cells seen in polymorphous low-grade adenocarcinoma. Although both adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma show neural invasion, in polymorphous low-grade adenocarcinoma this is often associated with a striking whorling arrangement of single-file cords of cells or small ducts, and is seen predominantly within, or very close to, the main tumor mass. It has been postulated that staining with c-kit or galectin 3 aids the

distinction between polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma, but recent studies suggest the value of these immunoagents is limited (48,49). In addition, c-kit expression in adenoid cystic carcinoma does not appear to correlate with behavior (50,79). Occasional foci in pleomorphic adenoma can resemble adenoid cystic carcinoma but the presence of typical myxochondroid matrix and plasmacytoid or spindle-shaped cells helps to avoid confusion (80). Basaloid squamous cell carcinoma can resemble solid variants of adenoid cystic carcinoma but typically involves the hypopharynx and larynx, which are uncommon sites for adenoid cystic carcinoma. Both can show islands with cribriform configurations, hyaline material surrounding tumor nests, and solid areas with comedonecrosis, but basaloid squamous carcinoma also has evidence of squamous differentiation and usually involves the overlying mucosa. In addition, the different patterns of p63 staining may aid distinction (51). Both epithelial-myoepithelial carcinoma and the tubular variant of adenoid cystic carcinoma can show double-layered, duct-like structures with an abluminal layer of clear cells (see page 563).

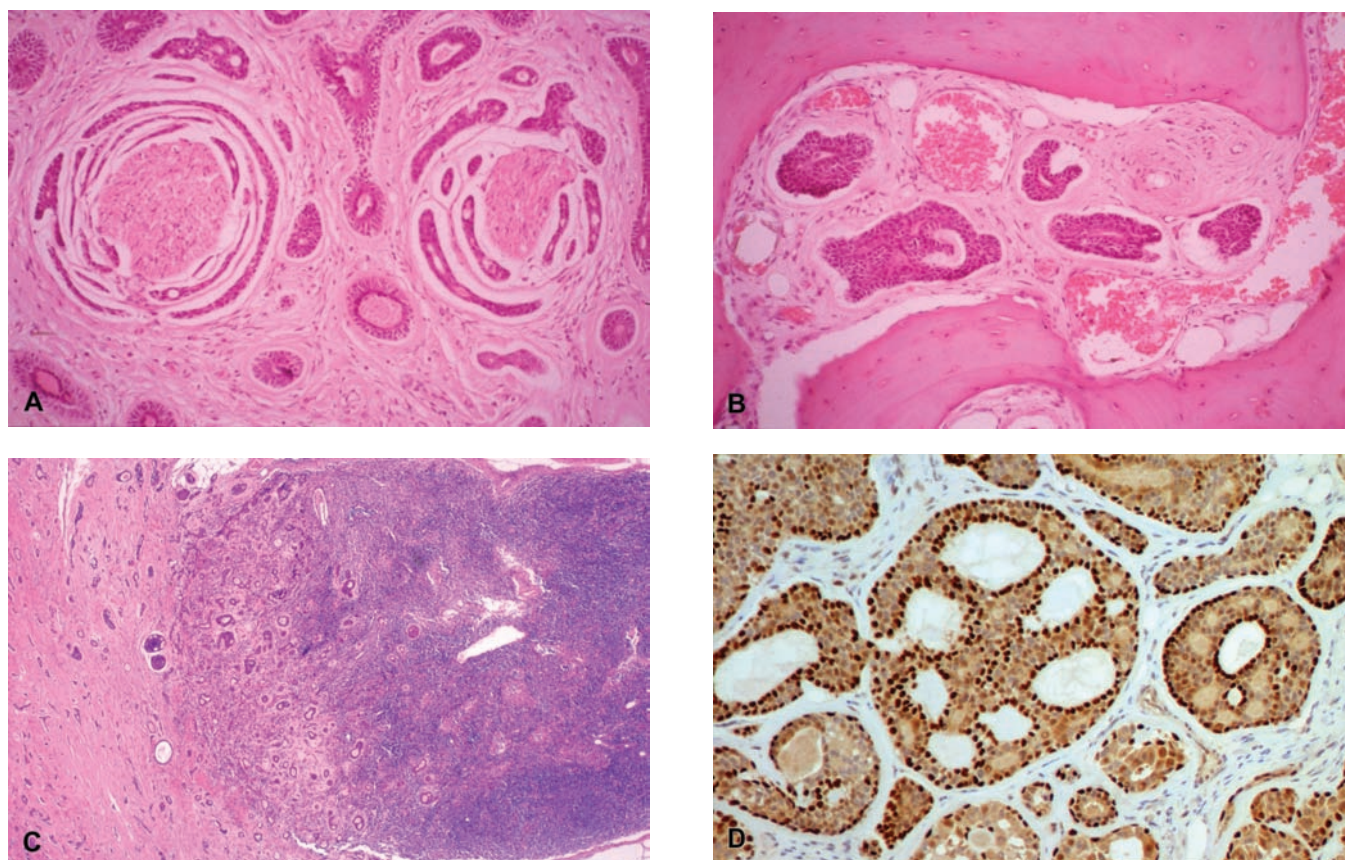


Figure 101 (A) Adenoid cystic carcinoma showing perineural invasion. (B) Adenoid cystic carcinoma showing bone invasion but absence of osteoclastic bone resorption. (C) Adenoid cystic carcinoma showing contiguous spread into a lymph node. (D) Adenoid cystic carcinoma. P63 staining of myoepithelial component.

Treatment and prognosis. The average 5- and 10-year survival rates are about 80% and 50%, respectively, but the majority of patients usually die of, or with, the tumor (81). Local recurrence is very common, especially in the first 5 years after surgery. The main prognostic factors are site, clinical stage, and histologic pattern (9,12,82). Tumors in the submandibular gland have a poorer prognosis than those in the parotid (83). Bone involvement and failure of primary surgery are associated with poor prognosis. Correlations between tumor morphology, grading, and outcome have yielded conflicting results, particularly after 10-year follow-up due to the overall poor long-term prognosis (81,83). The tubular and cribriform variants have been reported to have a better outcome than tumors with a solid component, especially if this exceeds 30% of the tumor volume (6,8,58,83–86). DNA studies have shown that there is a higher incidence of aneuploidy in solid tumors and this, not surprisingly, correlates with more aggressive behavior (87–89). High Ki-67 expression is also associated with solid and clinically more aggressive tumors (90). Tumors showing high-grade transformation (dedifferentiation) usually have a very poor prognosis (35–39).

The relationship between perineural invasion and survival is also contentious, but invasion of larger nerves appears to correlate with more aggressive behavior (14,85). In a review of the literature, Barrett and Speight (91) found 23% (range 2–86%) of patients had clinical evidence of neurologic deficit. Histologic evidence of perineural invasion was reported in 51% (range 8–86%) of cases. Clinical evidence of nerve involvement such as facial nerve palsy was an indicator of poor prognosis, but histologic evidence of perineural invasion appeared not to be an independent factor but was associated with other adverse features such as clinically large and more aggressive tumors. In addition, Spiro et al. in large follow-up studies of patients with adenoid cystic carcinoma found that both histologic grade and perineural invasion are unreliable predictors of behavior (9,82). Clinical stage is a better guide to prognosis (12,58). Lymph node involvement is relatively uncommon but distant metastases to lung, bone, brain, and liver are seen in 40–60% of cases (92).

Wide local excision, together with adjuvant radiotherapy, offers the best hope of local control (93,94). Elective neck dissection is not indicated. The

use of the tyrosine kinase receptor (CD117) inhibitor, Imatinib mesylate (95), and the dual inhibitor of the tyrosine kinase domains of the epidermal growth factor receptor and erbB2, Lapatinib (96), have not shown any significant clinical benefit.

Polymorphous Low-Grade Adenocarcinoma

Introduction. Polymorphous low-grade adenocarcinoma was first described as a distinctive minor salivary gland tumor by Evans and Batsakis in 1984 (1). Almost at the same time, this neoplasm was reported in two other publications as “terminal duct carcinoma” (2) and “lobular carcinoma” (3). The *WHO Classification of Salivary Gland Tumors* adopted the term polymorphous low-grade adenocarcinoma for this tumor, and it is now a well-recognized entity in the minor salivary glands (4). It has been defined as “a malignant epithelial tumor characterized by cytologic uniformity, morphologic diversity, an infiltrative growth pattern, and low metastatic potential” (4). Polymorphous low-grade adenocarcinoma is the second most common type of malignant neoplasm of minor salivary glands, after mucoepidermoid carcinoma (5,6), but is exceedingly rare in the major glands (7).

The 2005 WHO Blue Book introduced a recently described tumor, “cribriform adenocarcinoma of the tongue,” as a possible variant of polymorphous low-grade adenocarcinoma, but its relationship to this tumor remains controversial (4). The authors hypothesized that this tumor might be derived from the thyroglossal duct anlage. Only one series consisting of eight such cases has been reported (8). The tumor occurred in adults with a mean age of 50 years, and there was no gender predilection. Unlike typical polymorphous low-grade adenocarcinoma, all patients with this neoplasm had cervical lymph node metastases at the time of clinical presentation, but all were reported to be alive with no distant metastases after the initial surgery. Histologically, the tumor is characterized by predominantly solid and microcystic growth patterns composed of cells with pale, vesicular ground glass nuclei, closely resembling solid, and follicular variant of papillary carcinoma of the thyroid. On immunohistochemistry, cytokeratins and S-100 protein are strongly positive, whereas myoepithelial markers show only limited patchy positivity.

Clinical features. Polymorphous low-grade adenocarcinoma is one of the most common malignant neoplasms of the minor salivary glands. Over 400 cases of minor salivary gland, polymorphous low-grade adenocarcinoma have been reported (1,9–14). It accounts for approximately 10% of all intraoral minor salivary gland tumors, and 26% of all malignancies in these sites (6). Of the minor salivary gland cases, the palate is the most frequent site (12). Other minor salivary sites include the buccal mucosa, upper lip, retromolar region, and the base of the tongue. Among AFIP cases of minor salivary gland tumors, only pleomorphic adenoma and mucoepidermoid carcinoma are more common than polymorphous low-grade adenocarcinoma, and polymorphous low-grade adenocarcinoma is twice as frequent as adenoid cystic

carcinoma (5). Although there are several reports describing polymorphous low-grade adenocarcinoma of the major salivary glands, most of them are single cases, and there are very few histologically convincing examples. Only eight possibly acceptable polymorphous low-grade adenocarcinoma cases of major salivary gland origin, including three of our own proven cases, have been identified to date as far as we can judge from reviewing the literature (7). In the major salivary glands, polymorphous low-grade adenocarcinoma occurred in the parotid (5 cases), submandibular (2 cases), and sublingual (1 case) glands. The lacrimal glands, nasopharynx, and sinonasal cavity have also been rarely described as the site of the occurrence of polymorphous low-grade adenocarcinoma (15,16).

In the minor salivary glands, polymorphous low-grade adenocarcinoma has been reported to exhibit a nearly 2:1 female to male ratio and a wide age range (16–94 years) with a mean of 59 years (4). Several reports indicate that there are some differences in the occurrence of polymorphous low-grade adenocarcinoma among ethnic groups: there is a predilection for this tumor in blacks, while it is rare among Japanese (5,17). Polymorphous low-grade adenocarcinoma is generally an asymptomatic, slow-growing mass or swelling of the palate, cheek, or upper lip, occasionally associated with bleeding, telangiectasia, or ulceration of the overlying mucosa. Multiple, synchronous occurrence has been reported (18). Polymorphous low-grade adenocarcinoma may occur as a malignant component of carcinoma ex pleomorphic adenoma (19).

Pathology. Grossly, the tumor typically appears as a relatively well-circumscribed, tan-to-gray mass but with infiltrative margins. Tumor size ranges from 0.4 to 6 cm with an average of 2.2 cm (12).

Microscopically, the tumor invades into the salivary gland parenchyma (Fig. 102) and surrounding

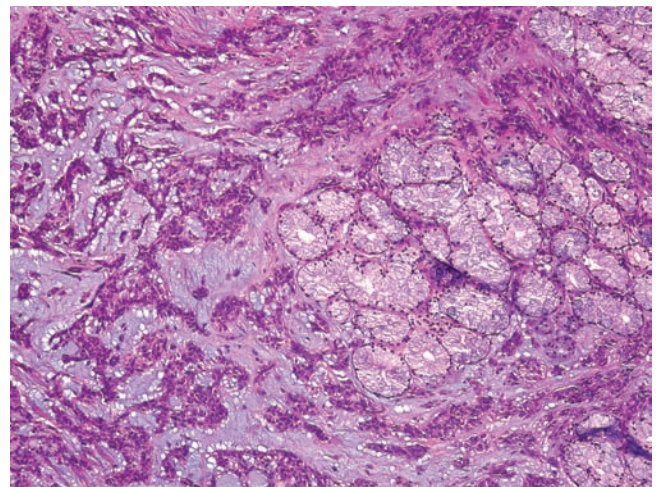


Figure 102 Polymorphous low-grade adenocarcinoma. Tumor invades into the minor salivary gland parenchyma.

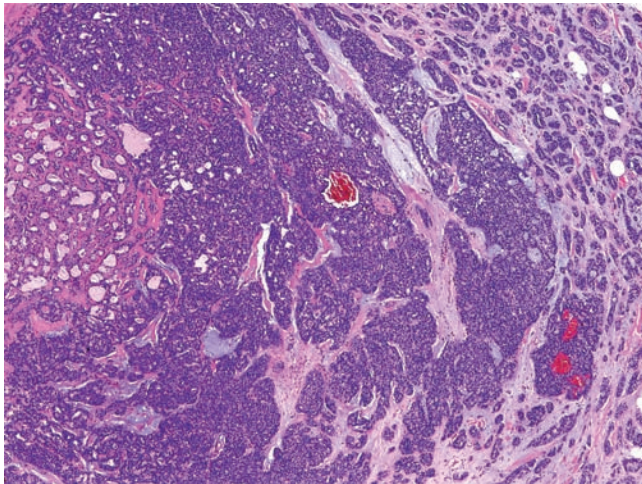


Figure 103 Polymorphous low-grade adenocarcinoma. Low-power view showing histologic diversity within the tumor. Mainly solid and tubular growth patterns with focal cribriform and papillary areas.

connective tissue close to the overlying mucosal epithelium and may even involve the underlying bone. The surface epithelium is usually intact, but is occasionally ulcerated. Polymorphous low-grade adenocarcinoma is often described as an architecturally diverse but cytologically uniform neoplasm within each case (Fig. 103). The tumor has a polymorphous growth architecture showing predominantly solid (Fig. 104A,B), tubular (Fig. 104C), fascicular (Fig. 104D), and cribriform (Fig. 104E) configurations with transitions between different patterns. Although papillary areas may also be observed focally (Fig. 104F), we recommend that tumors consisting almost exclusively of papillary areas should not be included in the category of polymorphous low-grade adenocarcinoma to prevent confusion with other entities, especially papillary cystadenocarcinoma, because they may have a different biologic behavior (20).

The solid portions often assume a lobular configuration, with nuclear palisading along the periphery of the tumor-cell nests. Tubular structures are predominantly lined by a single layer of small cuboidal cells. Both true tubular structures and pseudocystic spaces, with or without pale-staining amphophilic mucoid contents, result in a cribriform appearance. The areas showing a cribriform pattern are usually limited and do not predominate in polymorphous low-grade adenocarcinoma. Single-cell arrays of the tumor cells, termed an "Indian-file" arrangement, may be seen (Fig. 105A). Perineural invasion and association with small blood vessels, though true intravascular involvement is rare, are often detected as a concentric targetoid pattern consisting of streaming cords and narrow tubules of tumor cells (Fig. 105B). Tumor necrosis is absent or minimal.

The cytologic features of the tumor cells are uniform throughout the mass. They have small- to medium-sized, round to oval, fusiform nuclei without pleomorphism. Fusiform cells are often arranged in a fascicular pattern. The chromatin texture of the tumor cells is finely dispersed, and nucleoli are small and inconspicuous. The cytoplasm is relatively abundant and typically pale eosinophilic, but clear or oncocytic change may be focally observed, mainly in papillary areas. A few mucous cells, highlighted by mucin stains, may also be found. Mitotic figures are rare and atypical mitoses are absent. The tumors have hyalinized or mucoid stroma often with a blue-gray hue (Fig. 106), but no chondroid differentiation is demonstrated. Psammoma body-like microcalcifications and tyrosine-rich crystalloids may be present (21). A few examples of undifferentiated carcinoma or high-grade adenocarcinoma, evolving within a polymorphous low-grade adenocarcinoma, have been reported (22,23).

Immunohistochemistry. The tumor cells are positive for epithelial markers including low- and high-molecular weight cytokeratins and epithelial membrane antigen. Polymorphous low-grade adenocarcinomas are diffusely and strongly immunoreactive for S-100 protein and vimentin, whereas smooth muscle actin, muscle-specific actin, calponin, and glial fibrillary acidic protein are variably but usually uncommonly and focally expressed (11,12,24–27). Most tumors are diffusely positive for bcl-2 (11,12). The proliferative activity of the tumor cells assessed by Ki-67 labeling index is low (12,28).

Differential diagnosis. The most important differential diagnoses of polymorphous low-grade adenocarcinoma in the minor salivary glands are pleomorphic adenoma and adenoid cystic carcinoma.

Both polymorphous low-grade adenocarcinoma and pleomorphic adenoma share similar histologic features in terms of the diversity of growth patterns and the bland cytology. Although pleomorphic adenomas of the minor salivary glands are often nonencapsulated, they do not invade the surrounding salivary gland parenchyma and connective tissue. In addition, perineural invasion, a typical feature of polymorphous low-grade adenocarcinoma, is not seen in pleomorphic adenomas. If only limited biopsy material is available for examination, the differential diagnosis between the two neoplasms can be challenging. Polymorphous low-grade adenocarcinoma commonly exhibits hyalinizing or mucoid stroma as seen in pleomorphic adenoma, but plasmacytoid-type neoplastic myoepithelial cells and chondroid differentiation characteristic of pleomorphic adenoma are not a feature. Furthermore, tubular structures in pleomorphic adenoma are bilayered with ductal and myoepithelial differentiation, whereas they are usually formed by a single layer of cells in polymorphous low-grade adenocarcinoma. Immunohistochemical expression of glial fibrillary acidic protein is almost always observed in pleomorphic adenoma, while positivity is limited in cases of polymorphous low-grade adenocarcinoma (24,26).

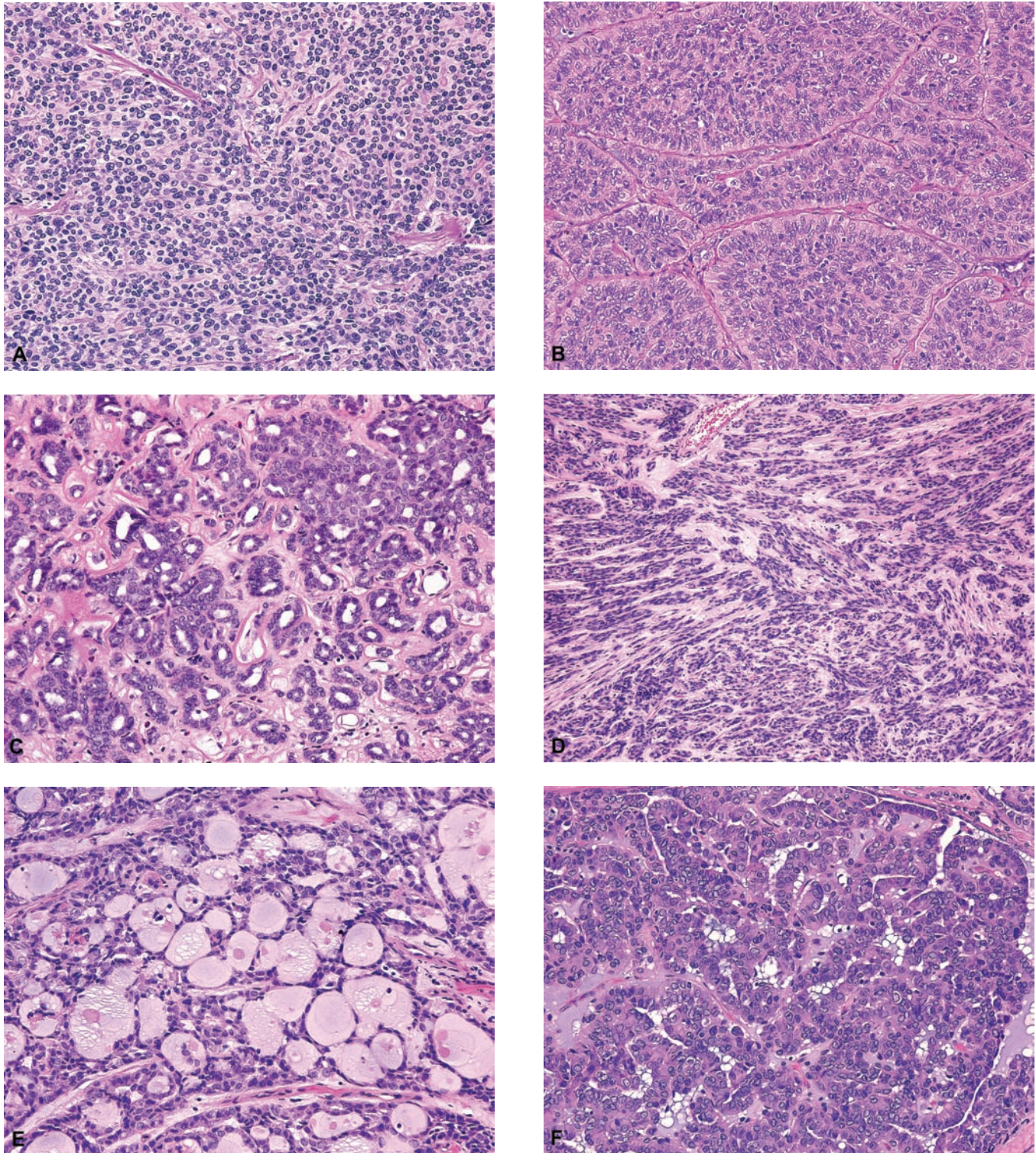


Figure 104 Polymorphous low-grade adenocarcinoma. Variable morphologic combinations of solid (**A** and **B**), tubular (**C**), fascicular (**D**), cribriform (**E**), and papillary (**F**) growth patterns. (**A**) Sheet-like solid growth of the tumor cells exhibiting uniform oval nuclei without any pleomorphism. (**B**) Lobular configuration with peripheral palisading arrangement. (**C**) Tubular structures are predominantly lined by a single layer of small cuboidal cells. (**D**) Fusiform cells are arranged in a fascicular pattern. (**E**) Multiple pseudocystic spaces with pale-staining amphophilic mucoid contents resulting in a cribriform appearance. (**F**) Papillary configurations of columnar or cuboidal cells.

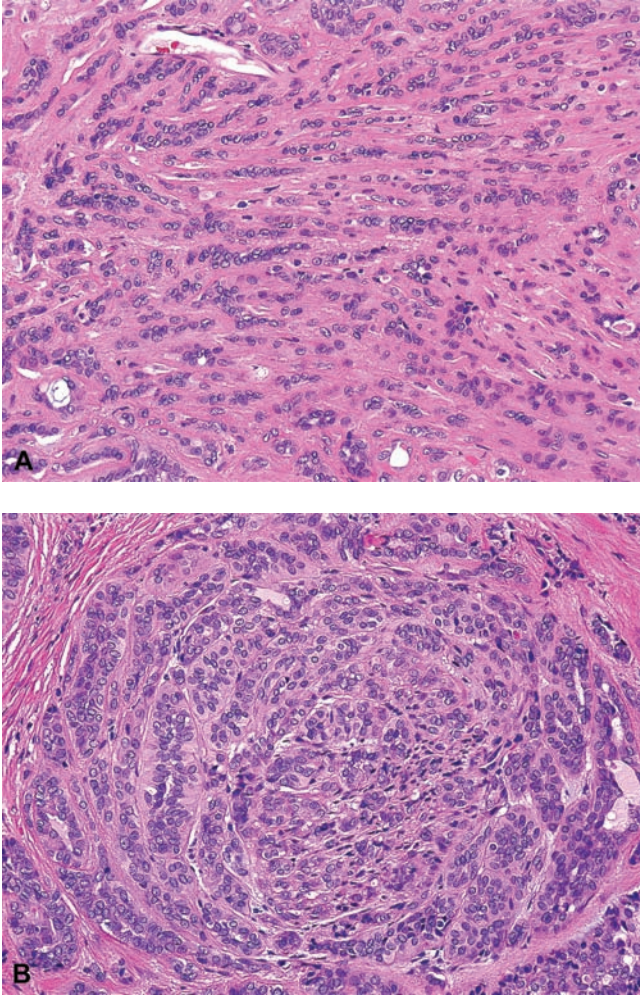


Figure 105 Polymorphous low-grade adenocarcinoma. (A) “Indian-file” growth pattern. (B) Perineural invasion with concentric targetoid appearance.

The distinction between polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma is also essential because of the significant difference in biologic behavior between these two entities. The distinction is mainly based on cytologic and architectural features. Round to oval, uniform nuclei with finely dispersed chromatin and more abundant cytoplasm in polymorphous low-grade adenocarcinoma contrast with the angular and hyperchromatic irregular nuclei and scant cytoplasm seen in adenoid cystic carcinoma. The cribriform pattern of adenoid cystic carcinoma is more rigid and commonly present than that of polymorphous low-grade adenocarcinoma. In addition, polymorphous low-grade adenocarcinoma lacks large pseudocystic spaces containing pools of basophilic glycosaminoglycans. Furthermore, tubules in polymorphous low-grade adenocarcinoma are typically lined by unilayered tumor cells, which contrast with the bilayered tumor cells seen in adenoid cystic

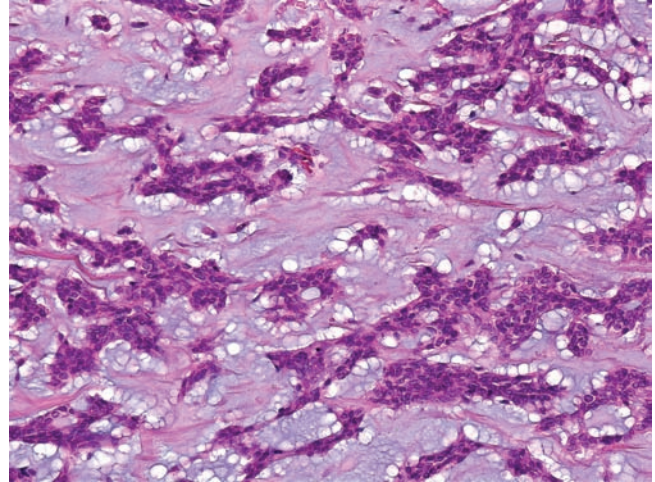


Figure 106 Polymorphous low-grade adenocarcinoma. Abundant mucoid stroma with a blue-gray hue.

carcinoma. One study has shown that the Ki-67 labeling index of adenoid cystic carcinoma (range 11.3–56.7%, mean 21.4%) is significantly higher than that of polymorphous low-grade adenocarcinoma (range 0.2–6.4%, mean 2.4%) without an overlap zone in their ranges (28). Immunoreactivity for S-100 protein is more diffuse and stronger in polymorphous low-grade adenocarcinoma than in adenoid cystic carcinoma. The value of c-kit expression in the differential diagnosis between polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma remains controversial (29,30).

Treatment and prognosis. Minor salivary gland polymorphous low-grade adenocarcinoma recurs locally and metastasizes to the cervical lymph nodes in 9% to 17% and in 9% to 15% of the patients, respectively, but very few patients have died from the disease (12,13). Local recurrence itself does not seem to be a major prognostic factor because no patients have died as a consequence. Distant organ metastasis is extremely rare (12,13). Polymorphous low-grade adenocarcinoma arising in the major salivary glands shares common clinical characteristics with tumors of minor salivary gland origin (7).

Surgical resection with an appropriate safety margin is the treatment of choice for polymorphous low-grade adenocarcinoma. Elective neck dissection is not warranted unless the patients have clinical evidence of lymph node metastasis. There can be protracted periods between initial resection and recurrence, indicating the need for a long-term follow-up. Tumors with a predominant papillary configuration have been reported to have a higher incidence of cervical lymph node metastasis. Whether such tumors should be considered within the spectrum of polymorphous low-grade adenocarcinoma or deemed to be a separate entity, such as papillary

cystadenocarcinoma, remains controversial (10,12,13,31). Polymorphous low-grade adenocarcinoma rarely can transform to a high-grade carcinoma if untreated or radiated (22,23). These patients have a less favorable clinical outcome.

Epithelial-Myoepithelial Carcinoma

Introduction. Epithelial-myoepithelial carcinoma is defined as “a malignant tumor composed of variable proportions of two cell types, which typically form duct-like structures. The biphasic morphology is represented by an inner layer of duct-lining, epithelial-type cells, and an outer layer of clear, myoepithelial-type cells” (1). It has many synonyms that cover a wide variety of benign and malignant tumors including: clear cell adenoma (2,3), glycogen-rich adenoma (4), tubular carcinoma (5), clear cell myoepithelioma (5), glycogen-rich adenocarcinoma (6), clear cell carcinoma (7), epithelial-myoepithelial carcinoma of intercalated duct origin (8), and adenomyoepithelioma (9).

Clinical features. Epithelial-myoepithelial carcinoma is uncommon and represents about 0.5% to 1% of salivary gland tumors. There is a female predominance of about 2:1 and the age range is wide (6–92 years) with a mean age at diagnosis of about 60 years (8,10–14). The tumor is rare in children (12,14,15).

The parotid gland (75%) and submandibular gland (10–12%) account for most cases. In the major glands, the tumor usually presents as a slow-growing, painless mass and facial nerve palsy is uncommon. It occasionally arises in oral minor salivary glands, particularly in the palate and tongue, and very rarely involves seromucous glands in the upper (8,11–13) and lower respiratory tracts (16–19); in these sites there is a tendency for the tumors to ulcerate. Involvement of the sublingual and lacrimal glands is exceptional. Adenomyoepithelioma is a histologically identical tumor that arises in the breast (20).

Pathology. Macroscopically, epithelial-myoepithelial carcinomas are usually well defined, firm swellings that are frequently nodular or multinodular. About a third of cases are encapsulated and areas invading the surrounding gland are not commonly seen. The cut surface is yellow to gray-white and cystic areas are common. Most tumors are 2 to 8 cm in diameter with a mean of about 3 cm (14) but larger examples have been reported (13).

The characteristic microscopic feature of epithelial-myoepithelial carcinoma is the formation of double-layered, duct-like structures. The luminal cells are typically arranged as single, cuboidal, or columnar luminal cells that have a central round or oval nucleus with finely granular, densely eosinophilic cytoplasm (Figs. 107–109). The polygonal abluminal cells form single or multiple layers and have clear cytoplasm and vesicular, eccentrically placed nuclei. The proportion of these two cell types and their morphologic distribution is widely variable. The duct-like structures may be separated by dense fibrous tissue but aggregated into theques or nests. In other areas,

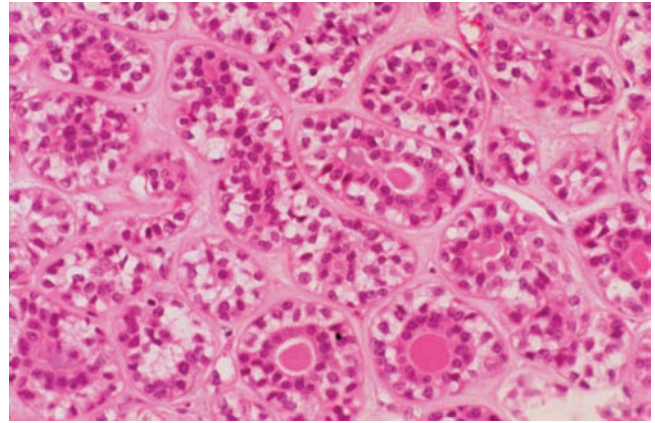


Figure 107 Epithelial-myoepithelial carcinoma showing double layered duct-like structures separated by acellular fibrous tissue.

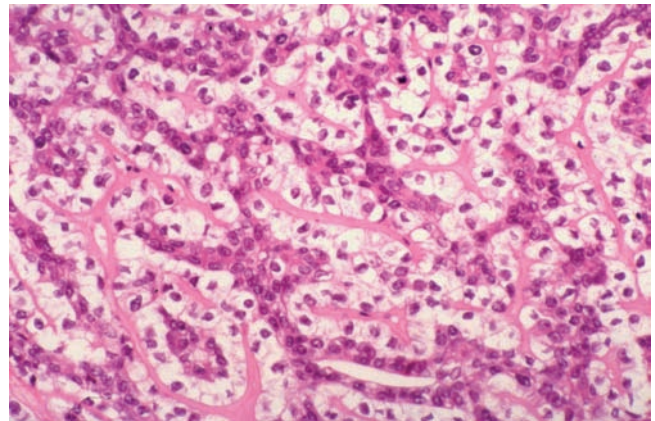


Figure 108 Epithelial-myoepithelial carcinoma with trabecular arrangement and predominantly noncanalized ducts.

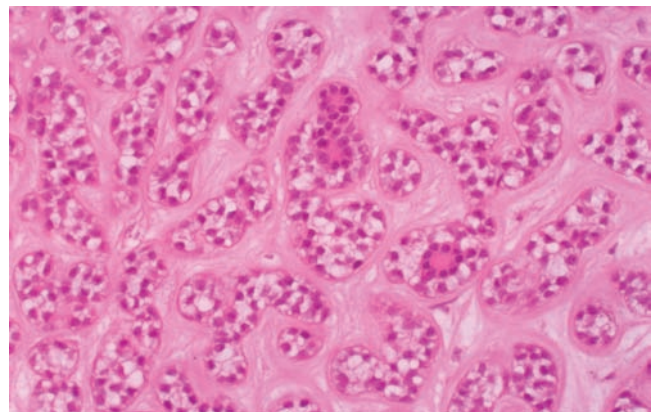


Figure 109 Epithelial-myoepithelial carcinoma consisting predominantly of nests of clear cells with scanty luminal cells.

although the nesting arrangement persists, the tumor forms cohesive sheets. Where the clear cell component predominates, the ductal configuration may not be initially obvious. In some tumors, the inner duct-lining cells do not canalize and are solid. Sometimes the inner and outer layers are composed of morphologically similar cells that do not have clear cytoplasm. Conversely, double clear cell-layered epithelial-myoepithelial carcinomas have recently been described (14). Cystic or papillary areas are present in about 20% of cases. Uncommonly there is squamous or oncocytic metaplasia, usually of the duct-lining cells. Very rarely spindle cell proliferation and "Verocay-like" palisading, similar to that occasionally seen in pleomorphic adenomas, has been reported. Sebaceous differentiation was described in 8/61 cases of epithelial-myoepithelial carcinoma in a recent study and was often associated with areas of oncocytic metaplasia (14). Several cases of epithelial-myoepithelial carcinoma showing sebaceous differentiation have been reported, and termed "sebaceous epithelial-myoepithelial carcinoma" (21). Mitoses are usually sparse in epithelial-myoepithelial carcinoma and rarely exceed 2 to 3 per 10 HPFs. Despite the relatively bland cytologic features, tumor necrosis is not uncommon. Only a small minority of tumors shows an infiltrative growth pattern but perineural invasion is present in about 30% of cases (Fig. 110) and angiolymphatic involvement is seen in about 10%. Dedifferentiated epithelial-myoepithelial carcinomas show greater cytologic atypia, higher mitotic frequency, and may have extensive areas of necrosis (14,22–25). There are two reported examples of epithelial-myoepithelial carcinomas with myoepithelial cell anaplasia characterized by severe nuclear atypia, pleomorphism, and hyperchromasia (14). Epithelial-myoepithelial carcinoma can develop in a pleomorphic adenoma (26) and may be a component of a hybrid tumor, particularly in combination with adenoid cystic carcinoma (27–32). In addition, epithelial-

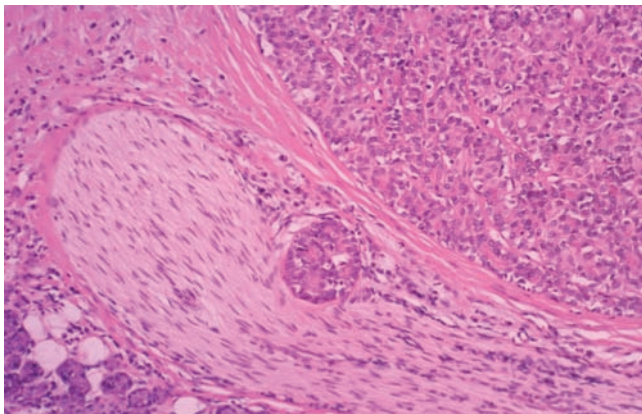


Figure 110 Epithelial-myoepithelial carcinoma showing neural invasion.

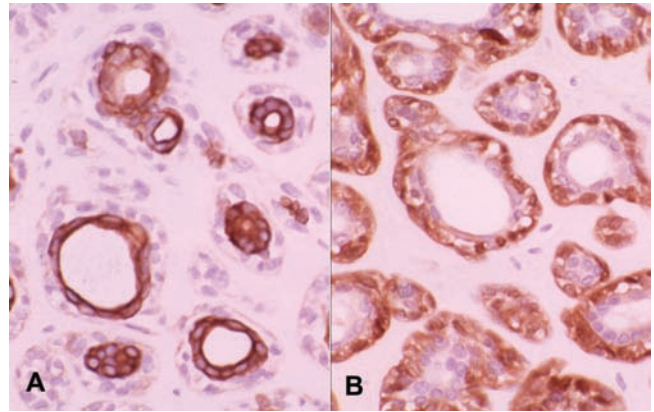


Figure 111 (A) Cytokeratin stain highlighting the luminal cells. (B) Calponin staining highlighting abluminal myoepithelial cells.

myoepithelial carcinoma is the tumor most commonly associated with ductal adenomatoid hyperplasia (intercalated ductal hyperplasia) (33,34).

Immunohistochemistry. The immunoprofile of epithelial-myoepithelial carcinoma corresponds to the biphasic nature of the tumor. Low-molecular weight cytokeratins such as AE1/AE3 and CAM 5.2 are strongly positive in the duct-like cells (Fig. 111A). They can also be detected in the clear cell population, though with lower staining intensity. "Myoepithelial markers" (p63, S-100 protein, alpha smooth muscle actin, calponin (Fig. 111B), vimentin, glial fibrillary acidic protein, smooth muscle myosin heavy chain) stain the clear cell compartment variably, with p63 probably being the best marker for these tumors (14). Bcl-2 is frequently positive and stains both duct-lining and myoepithelial cells, and c-kit, when positive, only stains the epithelial component (14). Tumors may show a relatively high Ki-67 proliferation index (~17%), typically in the myoepithelial component.

Molecular-genetic data. There are very few studies on the molecular-genetic characteristics of epithelial-myoepithelial carcinoma. Of those tumors karyotyped, half were normal and the remainder showed nondistinctive chromosomal abnormalities (35–37). Loss of heterozygosity has been shown in a single case of epithelial-myoepithelial carcinoma, in both the primary tumor and a metastatic deposit (38). The tumor examined had a double-layered, tubular growth pattern and a solid, predominantly myoepithelial component. Loss of heterozygosity at 13q12 and 18q21 was found in both architectural areas of the primary tumor and lymph node metastasis. In addition, loss of heterozygosity at 9p22-p21 and 10q23-q24 was shown predominantly in the solid part of the primary tumor and the metastasis, which was also solid, underlining distinct biologic differences in the two parts of the tumor.

Differential diagnosis. The differential diagnosis of epithelial-myoepithelial carcinoma includes tumors showing the formation of double-layered, duct-like structures and those consisting predominantly of clear cells. Double-layered, duct-like structures can be seen in pleomorphic adenoma and the tubular variant of adenoid cystic carcinoma. In these tumors the clear cells tend to have less abundant cytoplasm and their nuclei are usually hyperchromatic and angular. However, these variants usually only form focal areas of more typical tumors and the main problem arises in the interpretation of limited biopsy material. In such circumstances it may not be possible to distinguish between these three tumor-types with confidence and a circumspect report may be necessary. Some epithelial-myoepithelial carcinomas consist almost entirely of clear cells and it may require extensive sampling to identify characteristic double-layered ducts or obvious duct-lining cells. A wide range of benign and malignant salivary tumors can show focal or extensive areas consisting predominantly of clear cells. These include clear cell variants of pleomorphic adenoma, myoepithelioma, oncocytoma, mucoepidermoid carcinoma, acinic cell carcinoma, sebaceous neoplasms, and clear cell carcinoma (NOS). Clear cells in pleomorphic adenoma are usually focal and readily identified, but epithelial-myoepithelial carcinoma may be a component of carcinoma ex pleomorphic adenoma. In epithelial-myoepithelial carcinomas the clear cells are positive for glycogen and myoepithelial markers and unlike mucoepidermoid carcinomas they are mucicarmine negative and intermediate cells are not seen. Clear cells in acinic cell carcinoma are usually focal and the distinction is rarely problematical. Similarly, in sebaceous tumors, most of the cells have foamy rather than clear cytoplasm, although focally there may be genuinely clear cells. In clear cell oncocytomas, phosphotungstic acid hematoxylin positive granules can usually be identified in at least some of the cells. Clear cell carcinoma (NOS), including the hyalinizing variant, lacks the biphasic pattern of epithelial-myoepithelial carcinoma and usually stains negatively, or weakly, for myoepithelial markers. In addition, metastases from the kidney and thyroid gland may need to be considered by staining for CD10, renal cell carcinoma marker or thyroglobulin, or by using ultrasound as appropriate. Myoepithelial markers are helpful in distinguishing epithelial-myoepithelial carcinoma showing sebaceous differentiation from sebaceous carcinoma (21).

Treatment and prognosis. Despite its relatively bland cytologic features, epithelial-myoepithelial carcinoma is a low- to intermediate-grade tumor. Local recurrence is common but rates in the literature are variable and range from 23% to 80% (14) with a mean of about 30%. The incidence of metastasis to regional lymph nodes and distant sites such as lung, liver, and kidney, also shows a wide range, varying from 5% to 25% of cases. Despite this, the prognosis is relatively good and in one large study the disease-specific survivals were 93.5% at 5 years and 81.8% at 10 years (14). Margin status is the most significant pathologic prognostic factor. Incomplete surgical excision is

associated with recurrence and metastasis (8,10–14). The poorer prognosis seen in tumors located in minor salivary and sero-mucinous glands may be because of a higher frequency of recurrences resulting from incomplete excision (1). In a recent large study, no cases that were encapsulated or were minimally invasive recurred (14). Size and rapid tumor growth may be associated with a worse prognosis (20,22) but some studies have failed to show this correlation (14). No correlation was found between proliferative activity and histologic pattern and prognosis in a cytophotometric study (39). Other factors associated with poorer prognosis include angiolymphatic invasion, necrosis, and myoepithelial anaplasia. The presence of nuclear hyperchromasia and irregularity in over 20% of tumor cells has been associated with more aggressive behavior (13). In addition, aneuploidy and high mitotic counts have been reported in cases with unfavorable prognosis (13). Although areas of dedifferentiation have been related to poor prognosis (22,23), this has not been universally confirmed (14); the size and distribution of such areas may be important in determining outcome.

The treatment of choice is complete surgical removal with neck dissection only when there is evidence of regional lymph node metastases. Adjuvant radiotherapy has no proven role.

Clear Cell Carcinoma, Not Otherwise Specified

Introduction. Clear cell carcinoma, not otherwise specified (NOS), has been defined as “a malignant epithelial neoplasm composed of a monomorphous population of cells that have optically clear cytoplasm with standard hematoxylin and eosin stains. Because many types of salivary gland neoplasms commonly or consistently have a component of clear cells, clear cell carcinoma is distinguished by the absence of features characteristic of these neoplasms and its monomorphous population of clear cells” (1). Synonyms include clear cell adenocarcinoma, glycogen-rich clear cell carcinoma, and hyalinizing clear cell carcinoma.

Clinical features. Clear cell carcinoma is an uncommon salivary tumor that is found predominantly in the minor glands of the mouth (~60%), particularly in the base of tongue and palate (2–4). Other sites include the lip, buccal mucosa, floor of the mouth, retromolar trigone, and tonsil. There is a single reported case involving the gingiva (4). The tumor is less common in the parotid (~28%) and submandibular (~12%) glands (2,5,6). Cases developing intraosseously within the maxilla and mandible have been reported (7). Clear cell carcinoma can form the malignant component of carcinoma ex pleomorphic adenoma (8). The majority of clear cell carcinomas arise in the 40 to 70 year age range with a mean of 58 years and they are rare in children (2,9). There appears to be no significant sex predilection. Tumors usually present as a nondescript, painless swelling but there may be ulceration and pain in tumors involving mucosal glands. Palatal tumors can invade the underlying bone (10).

Pathology. Most tumors are 3 cm or less in maximum diameter and the cut surface is typically grayish white. The tumor may appear well or poorly circumscribed but they are not encapsulated and they infiltrate the surrounding tissue. Microscopically, the tumor consists of a predominant population of round to polygonal cells of variable sizes with optically clear cytoplasm. The nuclei are usually round, have condensed chromatin, and may contain small nucleoli. They are eccentrically located. There may be mild-to-moderate nuclear atypia and a relatively high nuclear-cytoplasmic ratio, but mitoses are uncommon. The presence of intracytoplasmic glycogen can be demonstrated by staining with PAS, with and without diastase digestion, but the staining is variable in both distribution and intensity. Mucin stains are negative. In addition to the characteristic clear cells, there may be a minor population of smaller cells with pale, eosinophilic cytoplasm. The cells are aggregated into a variety of configurations including solid sheets, nests and trabeculae, and ductal differentiation is absent. Focal squamous metaplasia is an uncommon feature (6). In some tumors, the islands and nests are separated by thin, variably cellular, fibrous septa but many show densely sclerosed bands of collagen and constitute the "hyalinizing clear cell carcinoma" variant (Fig. 112) (11). The tumor invades the surrounding tissue, although this may only be in focal areas, and can show evidence of neural invasion. An aggressive variant of clear cell carcinoma with areas showing cytologic atypia, high mitotic frequency, and necrosis, has been reported (12).

Immunohistochemistry. Clear cell carcinomas have variable immunohistochemical profiles. They usually show diffuse or focal low-molecular weight cytokeratin staining but reactivity for vimentin, S-100 protein, glial fibrillary acidic protein, calponin, and actin is less predictable and often negative (4,6,10,11,13–16). It appears that the densely fibrous stroma seen in the hyalinizing variant is not formed by the accumulation

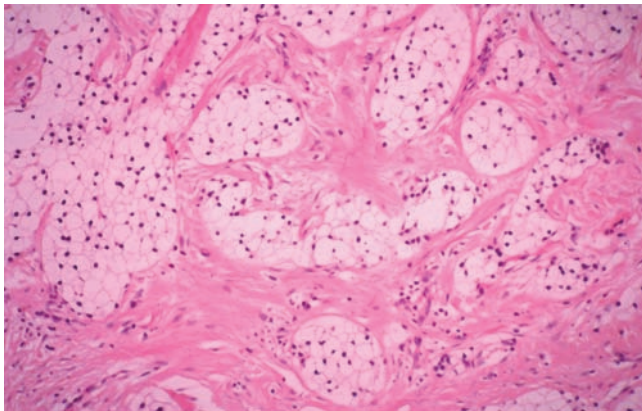


Figure 112 Hyalinizing clear cell carcinoma. Uniform population of cells with clear cytoplasm forming discrete nests in a dense fibrous stroma.

of basement membrane-type material, as it is composed mainly of type I collagen and fibronectin (17).

Differential diagnosis. The differential diagnosis of clear cell carcinoma (NOS) is considered in detail in the section covering epithelial-myoepithelial carcinoma (see page 562).

Treatment and prognosis. Most cases of clear cell carcinoma are low grade and the prognosis is excellent. They may show local recurrence but locoregional metastasis and distant spread are uncommon (4,6,11,18,19). A case of clear cell carcinoma with foci of less well-differentiated tumor showed widespread metastasis and death within a year of initial diagnosis (12). Complete surgical excision is the treatment of choice in the large majority of cases. Chemotherapy and radiotherapy have been occasionally used but their value is uncertain (12,19).

Basal Cell Adenocarcinoma

Introduction. Until recently, malignant basaloid salivary gland tumors have been variously referred to as basaloid salivary carcinoma (1), hybrid basal cell adenoma and adenoid cystic carcinoma (2), basal cell adenocarcinoma (3–11), basal cell carcinoma (12), basaloid carcinoma (13), and carcinoma ex monomorphic adenoma (14). Of these, there is now a clear consensus for the term basal cell adenocarcinoma, which is a distinct low-grade entity defined as a malignant counterpart of basal cell adenoma, designated by Ellis and Wiscovitch in 1990 (4). Furthermore, the basaloid tumor occurring in infants is probably best classified as sialoblastoma (15). Basal cell adenocarcinoma has similar demographic features and cytologic and architectural characteristics to those of basal cell adenoma but is an invasive tumor with potential for metastasis. The majority of basal cell adenocarcinomas arise *de novo* (4,7), but some develop via evolution from a preexisting basal cell adenoma, usually of the membranous variant (6,14,16).

Clinical features. Basal cell adenocarcinoma is a rare tumor, and slightly over than 100 cases have been reported (4–11). It accounts for less than 2% of all salivary gland tumors (15). Most basal cell adenocarcinomas have been reported to occur in the parotid and submandibular glands (4,6–8) but a few minor salivary gland cases have also been documented (5,9–11). There is no gender predilection and the peak incidence is in the sixth and seventh decades (range, 27–92 years; median, 60 years) (3). Most patients present with long-standing, painless swellings, but occasionally complain of pain or tenderness. Similar to membranous variant of basal cell adenoma, a diathesis of concurrent dermal tumors, especially eccrine cylindromas and trichoepitheliomas, has been documented in patients with basal cell adenocarcinoma, but its frequency is lower than that seen in individuals with basal cell adenoma (4).

Pathology. The tumor size of basal cell adenocarcinoma ranges from 0.7 to 7.0 cm with a mean size of 2.4 to 3.4 cm (3–11). Basal cell adenocarcinomas are usually unencapsulated with focal invasion into the

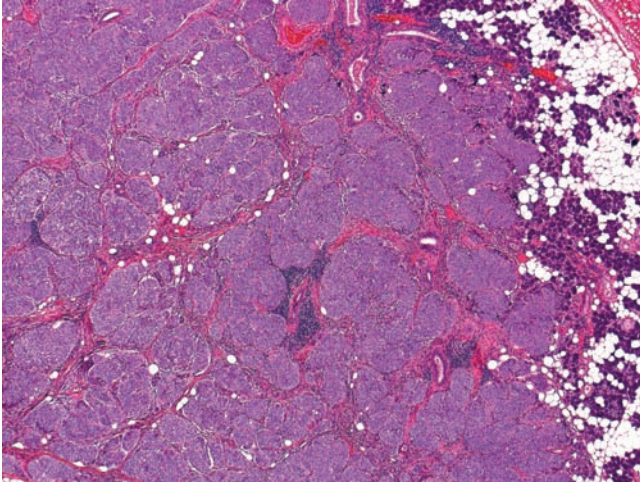


Figure 113 Basal cell adenocarcinoma. Low-power view showing tumor cell islands invading into the salivary gland parenchyma.

adjacent salivary gland or soft tissue, but some are well circumscribed.

Microscopically, the essential architectural pattern and cytologic appearance of basal cell adenocarcinoma resemble those of basal cell adenoma. However, unlike basal cell adenomas, which are always well circumscribed and encapsulated, all basal cell adenocarcinomas invade into the surrounding normal salivary gland parenchyma (Fig. 113) or adjacent soft tissue, though a few cases are focally encapsulated. As in basal cell adenoma, they can be generally divided into four subtypes: solid, trabecular, tubular, and membranous, according to its predominant histologic features (Fig. 114). The solid type of growth is the most common feature. Tumors with predominantly trabecular, tubular, or membranous pattern are uncommon. A palisade-like arrangement of the carcinoma cells is characteristic at the periphery of the tumor cell nests (Fig. 115), but this feature is less conspicuous than in basal cell adenoma. In the membranous type, PAS-positive basement membrane-like material surrounds individual tumor islands and is sometimes deposited within the tumor cell nests. Focal squamous differentiation with a whorling

pattern or eddies, or even forming keratin pearls, is sometimes seen (Fig. 116).

Two distinct cell populations, dark-staining basaloid cells and larger pale cells, are recognized in every case to varying extents depending on the growth pattern; the former cells are evident in solid and membranous variants and the latter cells mainly form ductal structures. Some basaloid tumor cells can evolve into spindle-shaped cells. Nuclear and cellular pleomorphism is usually slight but varies from case to case. Sometimes, the nuclear and cellular features are virtually indistinguishable from basal cell adenoma. In general, however, mitotic figures are easily identified in basal cell adenocarcinoma and the mitotic count is usually more than 4/10 HPFs. Necrosis is seen in a half of the tumors, either the comedo or spotty type. Vascular involvement is common and perineural invasion can also be identified.

Immunohistochemistry. Immunohistochemical and ultrastructural studies have shown that basal cell adenocarcinomas are composed of similar cell populations as basal cell adenomas with the dual ductal and myoepithelial phenotypes (8,17). Tumors are positive for cytokeratin and often focally immunoreactive for epithelial membrane antigen and carcinoembryonic antigen, indicating ductal differentiation. Myoepithelial markers, smooth muscle actin as well as S-100 protein and vimentin, are frequently expressed by abluminal cells located at the periphery of the tumor nests. The Ki-67 labeling index is usually higher in basal cell adenocarcinoma (more than 5%) than in basal cell adenoma (less than 2.7%) (7). Expression of p53 and epidermal growth factor receptor may be observed in basal cell adenocarcinoma, whereas these are both negative in basal cell adenoma (7).

Differential diagnosis. The differential diagnosis of basal cell adenocarcinoma includes basal cell adenoma, adenoid cystic carcinoma (especially of the solid type), small cell carcinoma, large cell neuroendocrine carcinoma, and basaloid squamous cell carcinoma (18).

Because of the frequent bland cytology of basal cell adenocarcinoma, it is often distinguished from basal cell adenoma by other histologic hallmarks such as invasive outgrowth, perineural and vascular invasion, necrosis, and mitosis (Table 8). Although immunohistochemical markers for myoepithelial differentiation are not useful in the differential diagnosis between the two neoplasms, demonstrating cell

Table 8 Comparison of Clinicopathologic Features of Basaloid Salivary Gland Tumors

	BCA	BCAC	Solid AdCC
Growth pattern	Encapsulated	Invasive	Invasive
P/eripheral palisading	Distinct	Distinct to vague	Inconspicuous
Atypia	Mild	Mild to marked	Marked
Mitosis	Few	Frequent	Numerous
Necrosis	No	Common (spotty)	Common (comedo)
Squamous differentiation	Occasional	Common (1/3)	No
Perineural invasion	No	Occasional (1/4)	Frequent
Vascular involvement	No	Occasional (1/4)	Frequent
Biologic behavior	Benign	Low-grade malignancy	High-grade malignancy

Abbreviations: BCA, basal cell adenoma; BCAC, basal cell adenocarcinoma; Solid AdCC, solid type of adenoid cystic carcinoma.

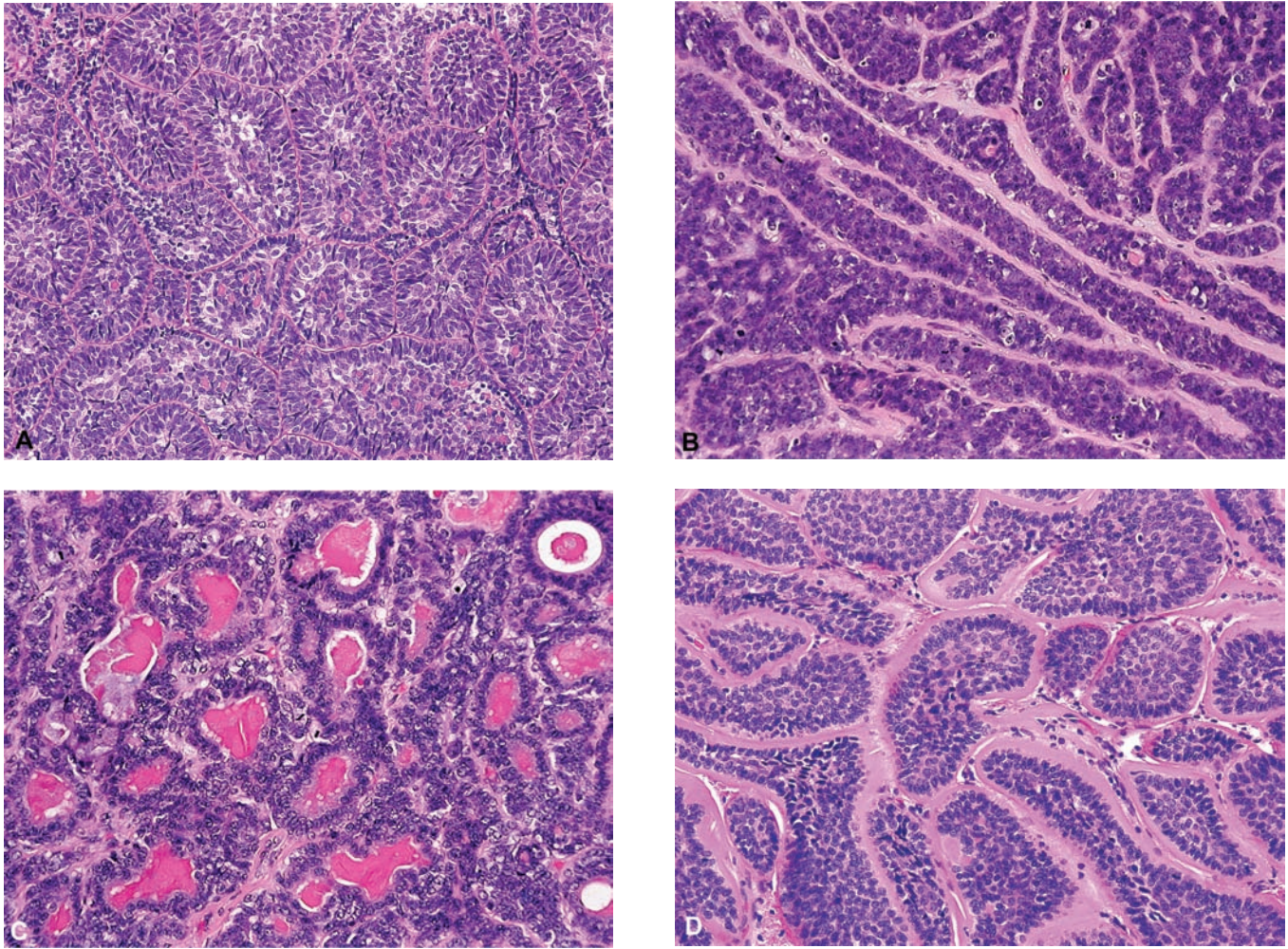


Figure 114 Basal cell adenocarcinoma. (A) Solid type. Note a palisade-like arrangement of the carcinoma cells at the periphery of the tumor cell nests. (B) Trabecular type. Cordlike architecture of the atypical basaloid cells. (C) Tubular type. Duct-like structures with intraluminal eosinophilic secretion. (D) Membranous type. Thick, hyaline, basement membrane-like material surrounds individual tumor islands.

proliferation index, apoptosis, expression of p53, epidermal growth factor receptor, and bcl-2 may be helpful (see the section “Basal Cell Adenoma”) (7).

The distinction between basal cell adenocarcinomas and the solid type of adenoid cystic carcinoma is also essential because of the significant difference in prognosis between these two entities (Table 8). The presence of peripheral palisading and foci of squamous metaplasia favor the diagnosis of basal cell adenocarcinoma. Even in the solid type, cribriform growth pattern and pseudocysts with amorphous basophilic material characteristic of adenoid cystic carcinoma is only rarely encountered in basal cell adenocarcinoma. In addition, tumor cell nuclei of adenoid cystic carcinoma tend to be more hyperchromatic and angular when compared with polygonal nuclei found in basal cell adenocarcinomas.

The lack of neuroendocrine differentiation and the presence of myoepithelial differentiation in basal

cell adenocarcinoma are points of difference from small or large cell neuroendocrine carcinoma, which may exhibit peripheral palisading patterns and comedo necrosis (19).

Basaloid squamous cell carcinoma is a specific clinicopathologic entity of high-grade malignancy, mainly arising in the hypopharynx, base of tongue, and supraglottic regions (20). Similar to basal cell adenocarcinoma, this malignancy may exhibit lobular growth pattern with peripheral nuclear palisading and often displays comedo necrosis. In basaloid squamous cell carcinoma, however, the tumor shows multiple attachments to the overlying epithelium. Definitive differential diagnosis is possible when absence of dual ductal and myoepithelial differentiation is confirmed immunohistochemically. Moreover, most basal cell adenocarcinomas arise in the major salivary glands, a site where basaloid squamous cell carcinoma does not occur.

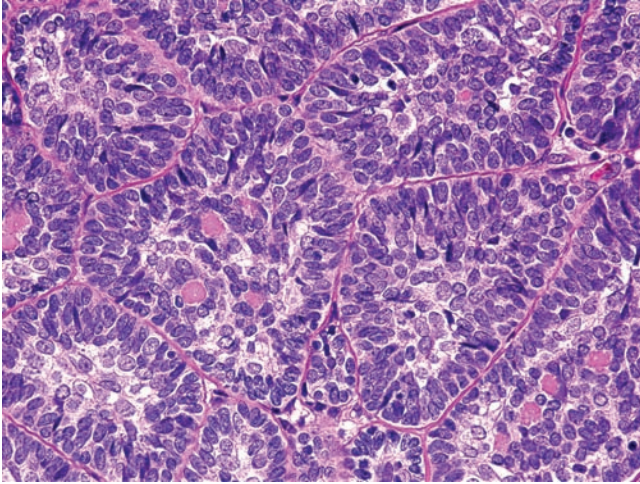


Figure 115 Basal cell adenocarcinoma. Solid nests of mildly atypical basaloid cells with peripheral palisading.

Treatment and Prognosis. In general, basal cell adenocarcinoma is considered to be a low-grade malignancy with a relatively high recurrence rate but good prognosis (4,6–8). Local recurrence in the major salivary gland cases occurs in about 40% of cases, but locoregional and distant metastases are infrequent, with less than 10% occurrence, and death from tumor is extremely rare. Basal cell adenocarcinoma arising in intraoral minor salivary glands or sino-nasal sero-mucinous glands appears to have a somewhat higher recurrence rate, and is accompanied by worse prognosis (5,9–11). Complete surgical excision is the recommended treatment. In major salivary gland cases, with proper surgical resection and adequate margins, additional therapy may not be required. Cervical lymph node dissection is not warranted, except for patients with clinical evidence of lymph node metastasis.

Sebaceous Carcinoma

Introduction. Sebaceous carcinoma is defined as “a malignant tumor composed of sebaceous cells of varying maturity that are arranged in sheets and/or nests with different degrees of pleomorphism, nuclear atypia, and invasiveness” (1). The term sebaceous adenocarcinoma has also been used (2).

Clinical features. Sebaceous carcinomas of salivary glands are very uncommon with about 30 reported cases arising from major glands (2–10). The large majority of these tumors developed in the parotid gland, with two cases in the submandibular gland (7,10) and a single case in the sublingual gland (1). Sebaceous carcinomas in the oral cavity may develop from Fordyce granules rather than intraoral minor glands (11) and probably should not be recorded as salivary tumors. Similarly, the histogenesis of rare cases reported in the vallecula, epiglottis, and hypopharynx is uncertain (12–14). There is a

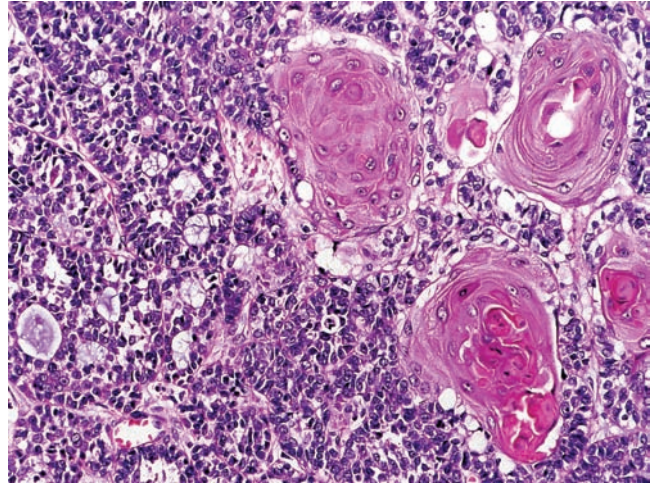


Figure 116 Basal cell adenocarcinoma. Focal squamous differentiation with keratin pearl formations.

bimodal age distribution with the incidence peaking in the third and seventh and eighth decades and there is a wide age range (17–93 years) (5). The mean age is 69 years and the sex distribution is equal. The duration of the tumor ranges from a few months to 20 years (8,15). Tumors typically present as slow-growing swellings with variable pain, facial nerve involvement, and fixation to the overlying skin. Rare cases have arisen from a preexisting pleomorphic adenoma (9).

Pathology. Grossly, tumors range in size from 0.6 to 8.5 cm and frequently appear to be well circumscribed or partially encapsulated (1). The color of the cut surface varies from yellow to pink, gray, or white. Microscopically, the tumor consists of sheets, nests, or cords of pleomorphic cells with variable degrees of cytologic atypia. In well-differentiated tumors, the cells have hyperchromatic nuclei and abundant, vacuolated cytoplasm giving a typical sebaceous appearance (Fig. 117). More poorly differentiated tumors have greater degrees of pleomorphism and may have clear or eosinophilic cytoplasm, making recognition of the sebaceous phenotype more difficult (Fig. 118). Duct-like structures may be numerous and cystic spaces of varying sizes are occasionally present. Scattered mucous cells are a rare feature. Squamous differentiation is common and basaloid differentiation can be seen, particularly in cells at the periphery of cellular islands. Spindle cell myoepithelial differentiation has also been reported (7). A xanthogranulomatous reaction to extravasated sebum and oncocytic metaplasia are occasional findings. In higher-grade tumors, particularly, there may be areas of necrosis and fibrosis. The tumor has infiltrative margins and perineural invasion is seen in about 20% of cases but vascular invasion is exceptional (5).

Treatment and Prognosis. There are too few recorded cases to make accurate prognostic statements. However, most tumors appear to be

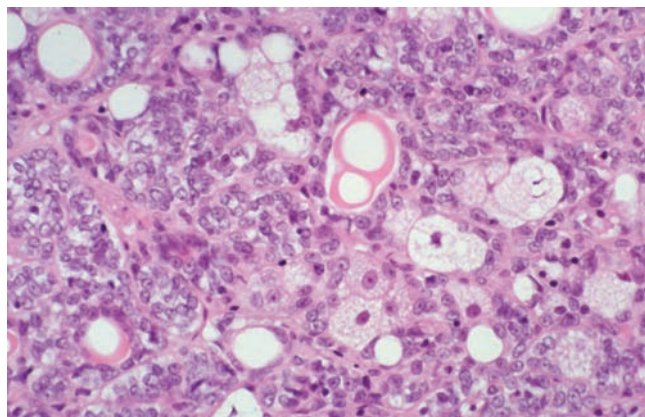


Figure 117 Well-differentiated sebaceous carcinoma consisting of non-specific glandular cells and cells showing conspicuous sebaceous differentiation.

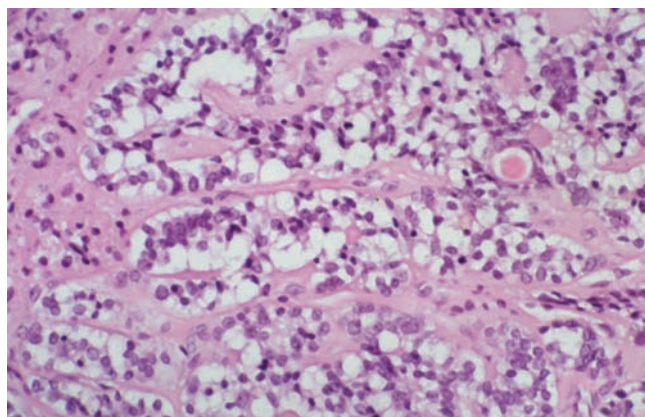


Figure 118 Another field from the tumor in Figure 117 showing clear cell change.

intermediate grade and have been treated by surgical excision, with or without postoperative radiotherapy. In tumors with a high microscopic grade or clinical stage, chemotherapy has occasionally been used in addition to adjuvant radiotherapy, but its value is debatable (4,5). It has been suggested that radical parotidectomy, together with elective neck dissection, should be considered in such tumors (2). About a third of tumors recur and the overall five-year survival rate is 62% (1).

Sebaceous Lymphadenocarcinoma

Introduction. Sebaceous lymphadenocarcinoma has been defined as "the malignant counterpart of sebaceous lymphadenoma. It is a carcinoma arising in a sebaceous lymphadenoma" (1). However, since this tumor was defined by the WHO, a case has been reported where the tumor developed from a lymphadenoma (2).

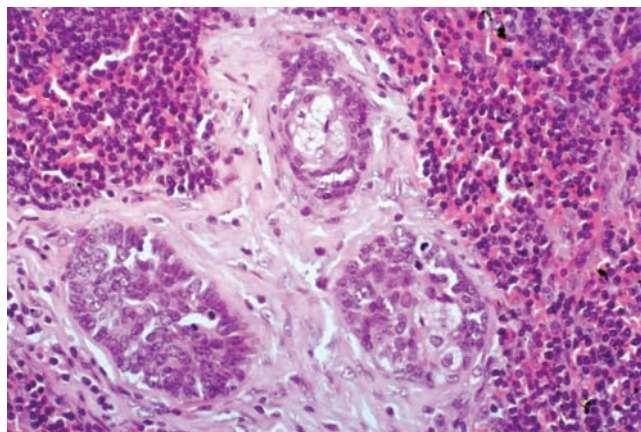


Figure 119 Sebaceous carcinomatous elements in dense lymphoid stroma.

Clinical features. Sebaceous lymphadenocarcinoma is the rarest salivary gland neoplasm with only five reported cases (2–5). Four cases arose in the parotid gland and one case involved a periparotid lymph node. There were four men and one woman and ages ranged from 55 to 70 years. The tumors were present from 1 month to more than 20 years and most formed painless masses.

Pathology. The tumors are grossly well circumscribed but show foci of local infiltration. The cut surface varies from yellow-tan to gray.

Microscopy of these cases has shown variable appearances. The tumors are partially encapsulated with areas of invasive growth and one case showed a subcapsular marginal sinus. They are usually composed of areas of typical sebaceous lymphadenoma with intermingled or sharply demarcated carcinomatous elements showing cytologic atypia with increased and atypical mitoses (Fig. 119). In one case the tumor appeared to arise from a lymphadenoma (2). The carcinomatous component has included sebaceous carcinoma with ductal differentiation or focally areas of poorly differentiated carcinoma, salivary duct carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma (1).

There may be areas of xanthogranulomatous inflammation. A single case showed evidence of neural involvement.

Treatment and Prognosis. Sebaceous lymphadenocarcinoma appears to be a low-grade malignant tumor with a strong tendency to local recurrence; distant metastasis is uncommon. It has been treated with wide surgical resection, with or without adjuvant radiotherapy.

Cystadenocarcinoma

Introduction. Carcinomas manifesting papillary-cystic morphology are relatively common in the ovary, bile duct, pancreas, breast, and thyroid.

However, cystadenocarcinoma arising in the salivary gland is a rare neoplasm that was first defined in the 2nd edition of WHO classification as a low-grade malignant tumor characterized by invasive growth and cystic architecture with papillary endocystic projections and was termed “papillary cystadenocarcinoma” (1). It has also previously been given various other names, including “malignant papillary cystadenoma” (2), “mucus-producing adenopapillary (non-epidermoid) carcinoma” (3,4), “low-grade papillary adenocarcinoma of the palate” (5,6), and “papillary adenocarcinoma” (7). In the 2005 WHO classification, this tumor was simply designated “cystadenocarcinoma” (8), because not all lesions have papillary configurations. It was defined as “a rare malignant tumor characterized by predominantly cystic growth that often exhibits intraluminal papillary growth. It lacks any specific histopathologic features that characterize the other types of salivary carcinomas showing cystic growth. Conceptually it is the malignant counterpart of the benign cystadenoma” (8).

Additionally, in the 2005 WHO classification, the tumor formally described as low-grade salivary duct carcinoma was included as a variant of cystadenocarcinoma and given the term low-grade cribriform cystadenocarcinoma (LGCCC) (9). This tumor type is discussed as a separate entity in this section.

Clinical features. Cystadenocarcinoma is rare, accounting for less than 1% of all salivary gland tumors. Approximately 65% arise in the major salivary glands, mostly in the parotid gland (10). The remaining 35% involve the minor salivary glands, including the lip, buccal mucosa, palate, tongue, retromolar area, and floor of the mouth, in descending order of frequency. There is a wide age range (20–86 years) with an average of about 59 years, and more than 70% of patients are over 50 years of age (10). Men and women are affected equally.

Most patients present with a slowly growing and asymptomatic mass, but rarely there may be pain and ulceration. When the tumor arises in minor salivary gland sites, the mucosal surface is usually intact, and the appearance clinically resembles a mucocele. Palatal tumors may erode the bone and infiltrate into the nasal cavity and maxillary sinuses.

Pathology. Macroscopically, cystadenocarcinoma appears as a partially circumscribed, multicystic mass, ranging in size from 0.4 to 6.0 cm with an average size of 2.4 and 2.2 cm in the major and minor salivary glands, respectively (10). Cystic spaces may contain clear-to-brownish or mucinous material. As the malignant counterpart of cystadenoma, microscopically, the essential architectural pattern of cystadenocarcinoma resembles that of cystadenoma. However, unlike cystadenomas, all cystadenocarcinomas invade into the surrounding normal salivary gland parenchyma (Fig. 120A) or adjacent soft tissue. Minor salivary gland tumors can infiltrate bone. Perineural and vascular invasion is uncommon.

The tumor is composed of multiple cysts. Each cystic space is separated by fibrous stroma, commonly with hemorrhage and inflammation because of cyst rupture. Psammoma bodies and microcalcifications

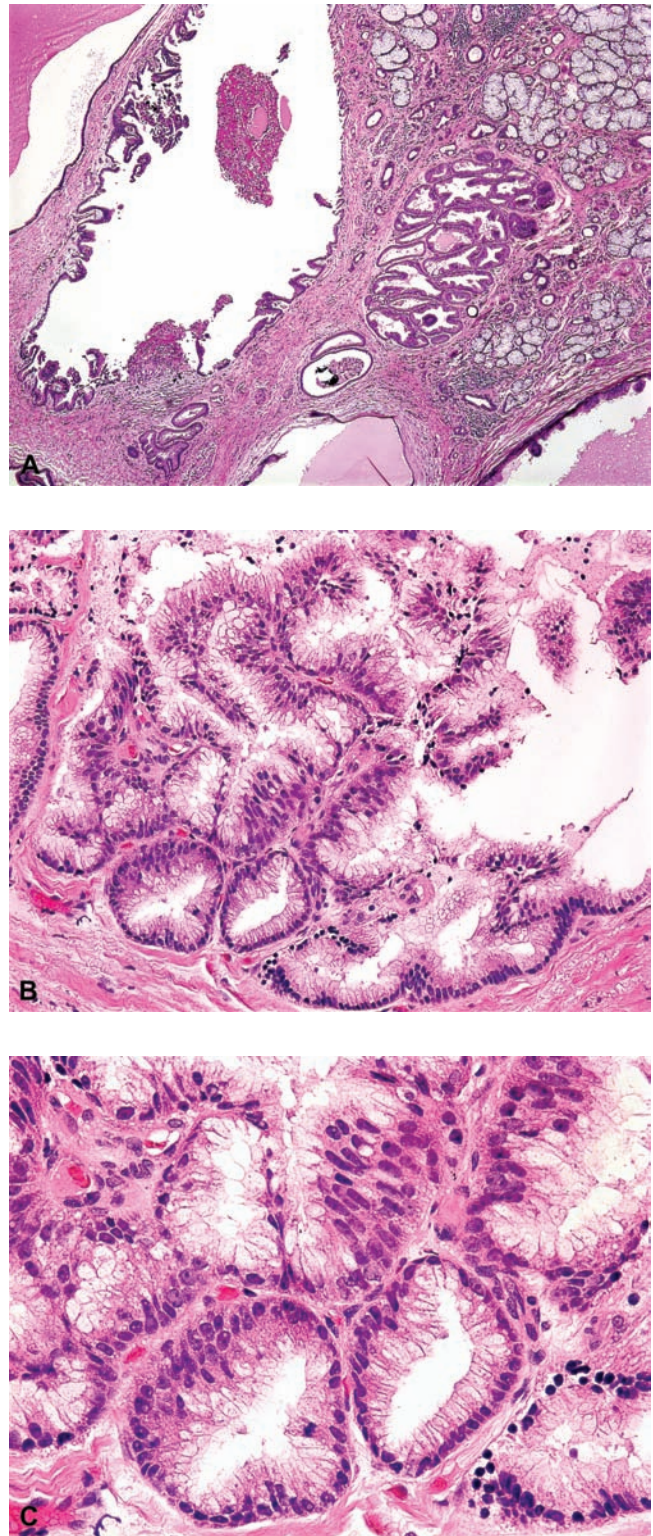


Figure 120 Cystadenocarcinoma. (A) Tumor with multiple papillary-cystic structures invades into the surrounding salivary gland parenchyma. (B) Cyst formations accompanied by prominent intracystic papillary projections of columnar cells. (C) Columnar tumor cells exhibiting mild nuclear pleomorphism. Source: Courtesy of Dr. Jean E. Lewis, Mayo Clinic, Rochester, Minnesota, U.S.A.

may be present. Cysts vary in size and shape and are usually accompanied by intracystic papillary projections with or without branching fibrovascular cores at least focally (Fig. 120B). About 75% of cases have a conspicuous papillary growth pattern (8). The term papillary cystadenocarcinoma is often applied to these tumors. Limited areas of ductal structures or small solid cells nests are seen in minority of the cases. The lining epithelium of the cysts, papillary fronds, and ductal structures are usually composed of a single cell layer, but may be double cell layered or pseudostratified.

In the majority of cases, the lining cells consist predominantly of small cuboidal cells, but large cuboidal, tall columnar, mucous, clear, oncocytic, and simple squamous cells can be seen, frequently with an admixture of these cell types. Usually, nuclear pleomorphism is mild to moderate and mitotic activity is low (Fig. 120C). However, occasional tumors have marked nuclear pleomorphism with prominent nucleoli and numerous mitotic figures (11,12). The columnar cells tend to show more nuclear atypia, suggestive of a relatively higher-grade malignancy than tumors consisting predominantly of cuboidal cells (10). Therefore, cystadenocarcinomas present a broader histologic spectrum than is generally thought, and at least some may be considered as high-grade malignancies.

Immunohistochemistry. The immunohistochemical features indicate that cystadenocarcinoma is composed of cells with ductal differentiation. The tumor cells are usually positive for pan-cytokeratin, epithelial membrane antigen, and carcinoembryonic antigen (13). CA19-9 and CA125 may be expressed in cystadenocarcinoma (14).

Differential diagnosis. The differential diagnosis of papillary cystadenocarcinoma includes salivary gland tumors with predominantly papillary and cystic pattern of growth, such as cystadenoma, low-grade mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma, the papillary-cystic variant of acinic cell carcinoma, salivary duct carcinoma, and metastatic papillary thyroid carcinoma (8).

Cystadenocarcinoma can have bland cytology and low mitotic activity, hardly distinguishable from cystadenoma, but unlike cystadenoma, cystadenocarcinoma always shows invasive growth.

Low-grade mucoepidermoid carcinoma is often composed of conspicuous multicystic and papillary structures, resembling cystadenocarcinoma. However, in contrast to cystadenocarcinoma, low-grade mucoepidermoid carcinoma has solid nests consisting of a mixture of epidermoid, mucous, and intermediate cells at least focally.

Like cystadenocarcinoma, areas of papillary and cystic proliferation are sometimes seen focally in polymorphous low-grade adenocarcinoma, but the predominant features of polymorphous low-grade adenocarcinoma are characterized by the admixture of variable histologic architectures, such as solid, tubular, fascicular, and cribriform patterns. In addition, perineural invasion is frequent in polymorphous low-grade adenocarcinoma, often with a concentric, targetoid pattern, but is uncommon in cystadenocarcinoma.

The papillary-cystic variant of acinic cell carcinoma may be difficult to distinguish from cystadenocarcinoma. Cystadenocarcinoma lacks microcystic or follicular growth pattern and the presence of cells with diastase-resistant PAS-positive secretory granules in the cytoplasm that are characteristic of acinic cell carcinoma.

The tumor cells of salivary duct carcinoma are larger and have more pleomorphic nuclei with prominent nucleoli and abundant eosinophilic cytoplasm and higher mitotic activity than those of cystadenocarcinoma. Furthermore, marked necrosis and a scirrhous invasive growth pattern are features distinguishing salivary duct carcinoma from cystadenocarcinoma.

Metastatic papillary thyroid carcinoma can be distinguished from cystadenocarcinoma by its characteristic ground-glass tumor cell nuclei, often with nuclear grooves and pseudonuclear inclusions, as well as positive immunostaining for thyroglobulin or thyroid transcription factor-1.

Treatment and prognosis. According to the AFIP series, in which follow-up data were available in 39 out of 57 cases of cystadenocarcinoma, no patients died of disease at a mean interval of 52 months after the initial surgery, 10% developed regional lymph nodal metastases at the time of diagnosis, and 7.7% had local recurrences at an average of 76 months after the initial treatment (10). These data suggest that cystadenocarcinoma is a low-grade malignancy. However, despite this there have been several reports indicating that some cases of cystadenocarcinoma may have more aggressive behavior and higher-grade pathologic features (11,12). The general therapeutic approach is complete local resection with cervical lymph node dissection, if there is lymphadenopathy, together with postoperative radiotherapy for high-grade or recurrent, inoperable tumors.

Low-Grade Cribriform Cystadenocarcinoma. LGCCC is a rare tumor first reported by Delgado et al. in 1996 as a variant of salivary duct carcinoma, termed low-grade salivary duct carcinoma (15). There are considerable histologic and biologic differences and controversies regarding the relationship between this tumor entity and conventional salivary duct carcinoma, which is a much more aggressive neoplasm (16,17). The 2005 WHO classification categorized low-grade salivary duct carcinoma as a variant of cystadenocarcinoma and adopted a new term LGCCC in an attempt to avoid confusion (9). However, because it bears a striking resemblance to atypical ductal hyperplasia or low-grade ductal carcinoma in situ of the breast, some investigators have strongly recommended that the term LGCCC should be replaced by "(low-grade) intraductal carcinoma" (18,19).

LGCCC almost exclusively occurs in the parotid gland, but in rare cases the submandibular gland and minor salivary glands may be affected (15,16,20). The majority of patients are in the sixth and seventh decades. Unlike salivary duct carcinoma, this tumor has a female predominance, the female to male ratio being 2:1 (9). Histologically, LGCCC is generally a well-circumscribed, but not encapsulated, tumor composed of multicystically dilated duct-like

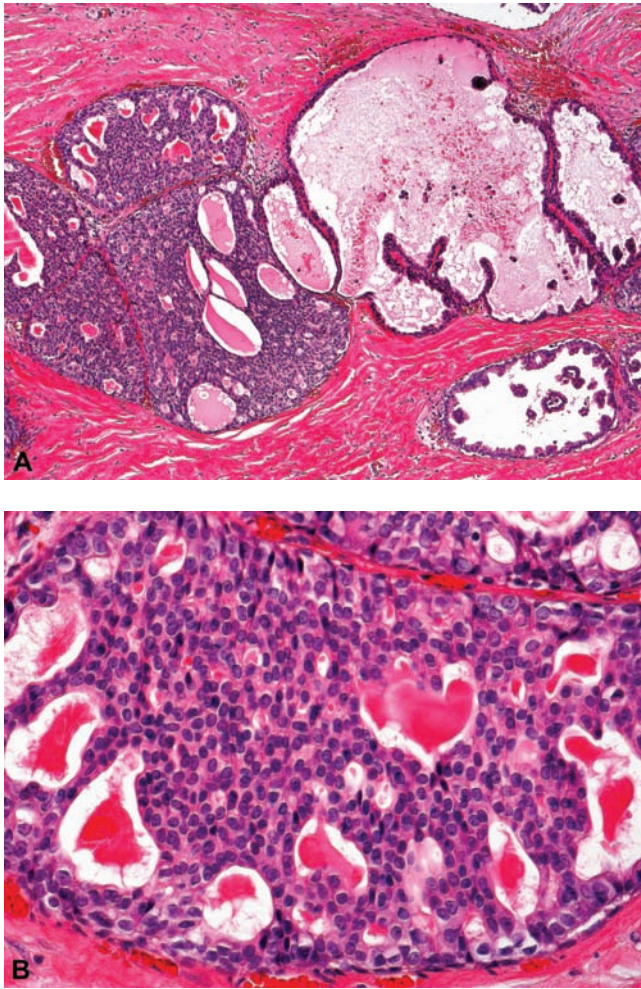


Figure 121 Low-grade cribriform cystadenocarcinoma. (A) Tumor composed of multicystically dilated duct-like structures accompanied by intraductal papillary proliferations and cribriform patterns. (B) Intraductal cribriform growth pattern of small and cuboidal or polygonal cells. Note that they are cytologically bland with finely dispersed chromatin and small nucleoli.

structures accompanied by varying degrees of intraductal proliferations (Fig. 121A). The lining cells of the dilated ducts are usually multilayered and form a combination of anastomosing micropapillae, plaque-like projections, tufts with thin delicate fibrovascular cores, and “floppy” fenestrated cribriform patterns (15,16). Separate, smaller ductal lesions tend to be filled with solid proliferation and cribriform structures of tumor cells.

Proliferating ductal cells are typically small and cuboidal or polygonal. They are cytologically bland with finely dispersed chromatin and small nucleoli (Fig. 121B). These histologic appearances are similar to those seen in atypical ductal hyperplasia or intraductal carcinoma of the breast. Tumor cells may show focal apocrine differentiation and the cytoplasm frequently has multiple, clear microvacuoles and a fine yellow-

to-brown pigment resembling lipofuscin. Mitotic figures are rare and necrosis is minimal or absent. Cellular pleomorphism is generally absent, but infrequently, a transition from low- to intermediate- or high-grade cytology with increased mitotic activity may be seen. These lesions may also be accompanied by focal invasion into surrounding tissue with small solid nests, reactive inflammation, and desmoplasia (16). The presence of microinvasion does not seem to affect prognosis. Usually there is no perineural or vascular invasion.

Unlike salivary duct carcinoma, LGCCC diffusely and strongly expresses S-100 protein on immunohistochemistry (Fig. 122A) (15,16). Intraductal tumor cell proliferation is outlined by myoepithelial markers (smooth muscle actin, calponin, cytokeratin 14, and p63)-positive nonneoplastic, myoepithelial cells (Fig. 122B) (16). The tumor cells are negative for both androgen receptor and HER2/*neu*.

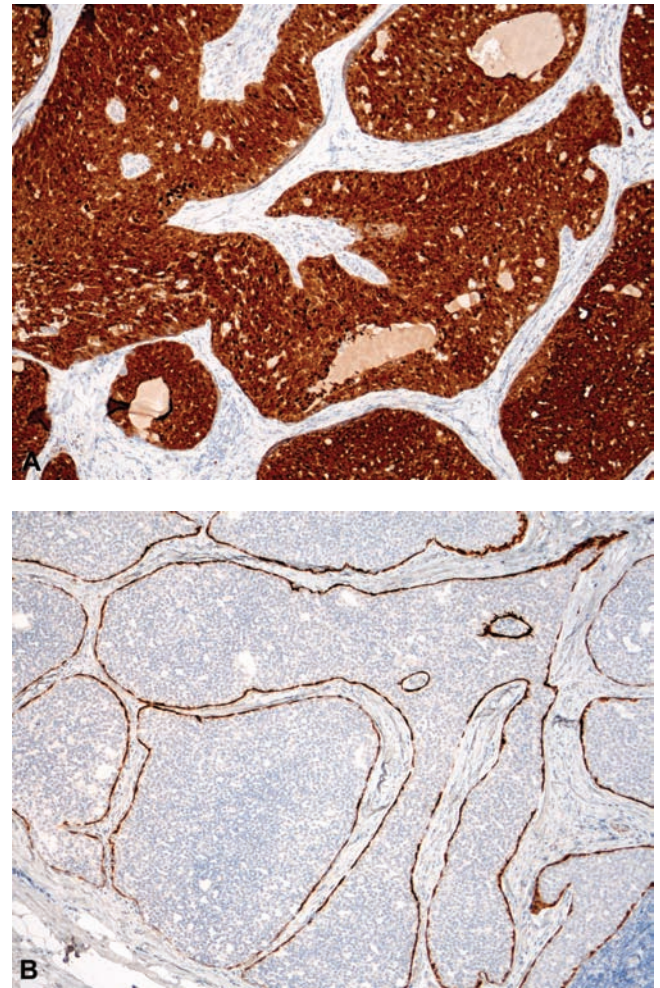


Figure 122 Low-grade cribriform cystadenocarcinoma. Immunohistochemistry. (A) Tumor cells diffusely and strongly express S-100 protein. (B) Intraductal tumor cell proliferation is outlined by calponin-positive non-neoplastic, myoepithelial cells.

The differential diagnosis of LGCCC includes the papillary-cystic variant of acinic cell carcinoma and conventional cystadenocarcinoma. It is often challenging to distinguish between the papillary-cystic variant of acinic cell carcinoma and LGCCC. Both tumors contain cells with vacuolar cytoplasm, but the vacuoles of LGCCC are smaller and refractile and are frequently associated with yellow-to-brown pigment. In addition, cells with diastase-resistant PAS-positive finely granular cytoplasm are only found in the papillary-cystic variant of acinic cell carcinoma, though the microvacuoles in LGCCC may also show diastase-resistant PAS staining. Cystadenocarcinoma does not resemble mammary atypical ductal hyperplasia or low-grade ductal carcinoma, and tends to be more invasive, while LGCCC is a usually a noninvasive lesion.

Complete surgical excision is the treatment of choice. The prognosis is excellent and none of the cases with follow-up have recurred (15,16,20).

Mucinous Adenocarcinoma

Introduction. Mucinous adenocarcinoma is defined as “a rare malignant tumor composed of epithelial clusters with large pools of extracellular mucin. The mucin component usually occupies the bulk of the tumor mass” (1). A commonly used synonym is colloid carcinoma.

Clinical features. This is a very rare salivary tumor and most examples have been reported as single cases or as short series. An analysis of 10 cases, including five from the literature (2), and a series of six cases published in the Chinese literature (3), together with four further cases (4–7) shows that patients’ ages ranged from 42 to 86 years with a mean age of about 65 years. There is no consistent sex predilection. About half the cases involved minor glands, particularly the palate; there were three cases each in the sublingual and parotid glands and two cases affected the submandibular glands (8). The usual presentation is a slow-growing mass of several months’ duration, but in one case the tumor had been present for 11 years. In the minor glands, tumors are firm and elevated and some are ulcerated. In tumors arising in the sublingual gland, a presumptive diagnosis of salivary calculi may be made.

Pathology. Tumors range in size from 2.5 to 7.6 cm and are usually bosselated and ill defined. The cut surface is grayish white and shows multiple cystic spaces containing gelatinous fluid.

Microscopically, the epithelial component consists of cells, which may be single or form duct-like structures or solid clusters of variable sizes. These are floating in abundant, mucus-filled lakes that are separated by fibrous septa (Fig. 123). The epithelial cells may be cuboidal, columnar, or irregular in shape (1). The cytoplasm is typically clear and there is a centrally placed, hyperchromatic nucleus. Although cells may show nuclear atypia, mitoses are infrequent. Some of the solid clusters of tumor cells may develop secondary lumina and scattered cells may have small

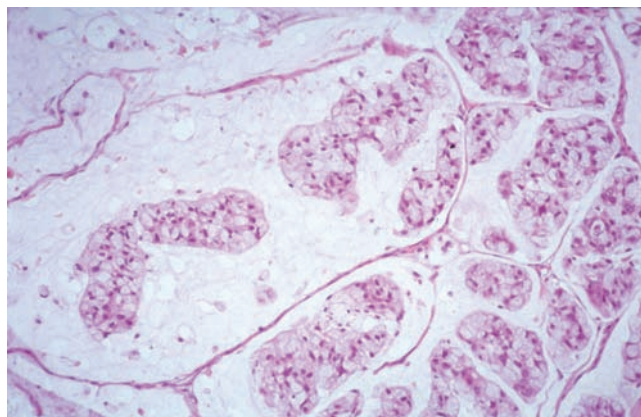


Figure 123 Mucinous adenocarcinoma. Nests of tumor cells floating in mucous filled, cystic space.

amounts of intracellular mucin. Mucin-containing cells may form papillary projections into the mucous pools or form acinus-like clusters. Focal necrosis is sometimes present. In a unique case of mucinous adenocarcinoma involving mandibular bone, neuroendocrine differentiation was demonstrated (7). The intra- and extracellular mucus stains positively with PAS, Alcian blue, and mucicarmine.

Immunohistochemistry. The limited number of immunocytochemical studies of mucinous adenocarcinoma show that the tumor is strongly positive for pan-cytokeratin (AE1/AE3) and cytokeratin 7 (3,4). Most tumor cells also express keratins 8, 18, and 19. There is minimal expression of keratins 4 and 13 and no expression of keratins 5/6, 10, 14, and 17. The tumor is also negative for smooth muscle actin, estrogen, and progesterone (4).

Differential diagnosis. The tumors to be considered in the differential diagnosis include mucoepidermoid carcinoma, cystadenocarcinoma, and the mucin-rich variant of salivary duct carcinoma (9). Although low-grade mucoepidermoid carcinomas frequently show extravasated mucous pools, the other characteristic features of the tumor make diagnostic confusion unlikely. The distinction from cystadenocarcinoma can be more problematical but in the latter, the tumor cells tend to line the cystic spaces and there is a lack of cell clusters floating in the mucous component. In the mucus-rich variant of salivary duct carcinoma, there are mucin lakes but there are also areas composed of the high-grade carcinoma cells typical of this tumor.

Treatment and prognosis. Surgery, with or without adjuvant radiotherapy, has been the treatment of choice in most cases, although the efficacy of radiotherapy has been questioned (1). There is a strong tendency for local recurrence and metastasis to regional lymph nodes. The tumor is aggressive, with about half the reported cases dying from the disease.

Oncocytic Carcinoma

Introduction. Oncocytic carcinoma is defined as “a proliferation of cytomorphologically malignant oncocytes and adenocarcinomatous architectural phenotypes, including infiltrative qualities. These may arise de novo, but are usually seen in association with preexisting oncocytoma” (1). Synonyms include oncocytic adenocarcinoma, malignant oncocytoma, and malignant oxyphilic adenoma.

Clinical features. Oncocytic carcinoma is one of the rarest salivary gland tumors with about 60 reported cases (2–21). The mean age is about 60 years and there is a wide age range (25–91 years). There is a male predominance of about 2:1 (3,7). The large majority arise in the parotid (~80%) and submandibular glands (~10%), with the remainder reported in a wide range of intraoral and upper respiratory tract sites. Clinically, oncocytic carcinomas usually present as painless, slow-growing swellings, but in about a third of cases there is pain or facial nerve palsy. In carcinomas arising in preexisting oncocytomas, there may be a history of a recent rapid enlargement of a long-standing swelling.

Pathology. Grossly, oncocytic carcinomas can appear as single or multifocal masses, which are firm, tan to gray-brown, and may show areas of necrosis. Some cases have variable capsulation but many tumors show extensive local invasion.

Microscopically, oncocytic carcinoma shows variable pleomorphism. Most consist of large tumor cells, which are round or polyhedral (Fig. 124). The cytoplasm is granular and eosinophilic and the round, vesicular, and centrally placed nuclei often contain one or more prominent nucleoli. There is usually a moderate mitotic frequency but in some cases, mitoses are numerous and there may be abnormal forms. Occasionally, multinucleated tumor cells are present. The tumor is arranged in sheets, nests, and trabeculae and infrequently there may be ductal differentiation. Some cases show focal areas of necrosis. There is usually widespread infiltration of the salivary gland

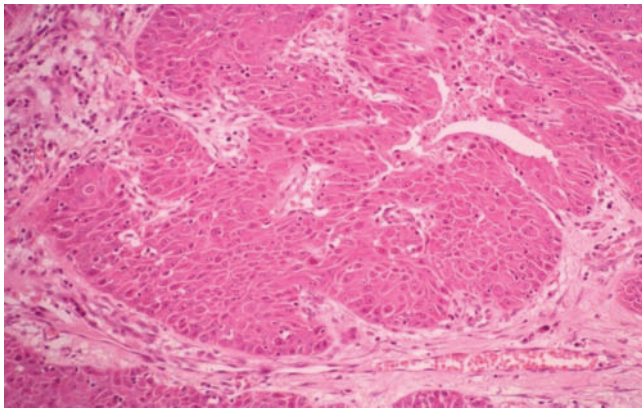


Figure 124 Oncocytic carcinoma showing cellular atypia and focal necrosis.

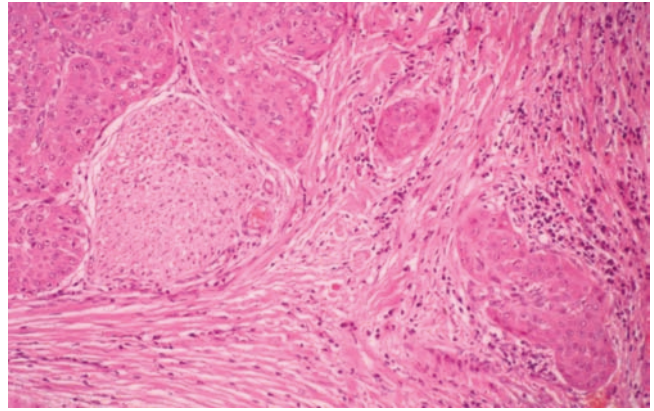


Figure 125 Oncocytic carcinoma showing neural invasion.

and surrounding tissue, and many cases show evidence of neural and vascular invasion (Fig. 125).

Immunohistochemistry. There is usually a higher Ki-67 proliferative index in oncocytic carcinoma than oncocytoma and this may be useful in differentiating the tumor from an atypical oncocytoma (21). Staining for alpha-1-antitrypsin (5) and antimitochondrial antibodies (22) has been reported.

Differential diagnosis. The main differential diagnoses include multifocal nodular oncocytic hyperplasia, oncocytoma, mucoepidermoid carcinoma, and salivary duct carcinoma. Multifocal nodular oncocytic hyperplasia can simulate an infiltrative tumor. This impression may be reinforced when there is age-related fatty change or when the oncocytic cells involve the hila of intraparotid lymph nodes. The multifocal nature of the hyperplasia and the presence of cytologically bland cells should prevent confusion. Oncocytomas show variable capsulation and occasionally there are atypical nuclei. In one study, benign oncocytomas were diploid but oncocytic carcinomas were associated with aneuploidy (23). In addition, oncocytomas show minimal or no mitotic activity and there is no evidence of invasion into salivary parenchyma. Although perineural invasion has been reported in benign oncocytomas (4), this observation has been disputed (3). Some mucoepidermoid carcinomas are almost entirely oncocytic (24,25) but the presence of intermediate cells and mucocytes aids diagnosis. Salivary duct carcinoma often consists of large, pleomorphic cells with eosinophilic, granular cytoplasm. However, there are duct-like structures and frequently luminal papillary ingrowths or cystic structures. In addition, the cells of salivary duct carcinoma are PTAH negative and are frequently androgen receptor positive (26).

Treatment and prognosis. Oncocytic carcinomas of the major salivary glands appear to be high-grade and aggressive from the outset, except in the rare cases where there was preexisting benign oncocytoma or multifocal nodular oncocytosis (8,27). They are locally infiltrative (8,9) and can show locoregional

lymph node metastases or widespread dissemination to the central nervous system, bone, liver, and lung (2,8–10,28). Some cases have a prolonged course with multiple local recurrences and distant metastases (8–10,27). In a review of the literature, 32% developed local recurrence and nearly 85% of oncocytic carcinomas developed regional or distant metastases (5). There is a high mortality (8), and in one survey, the average survival for patients with metastases was 3.8 years (4). Distant metastasis is the most important sign of poor prognosis, with all affected patients in one review dying of disease (7).

Oncocytic carcinomas should be treated by wide surgical excision. Due to the relative rarity of this tumor, the role of adjuvant radiotherapy is not firmly established. However, as the prognosis is known to be so poor, it should be strongly considered, together with the need for neck dissection.

Salivary Duct Carcinoma

Introduction. Salivary duct carcinoma is defined as “an aggressive adenocarcinoma that resembles high-grade breast ductal carcinoma” (1). It has intraductal and invasive components. Although many salivary carcinomas are postulated to originate from ductal cells and often demonstrate ductal structures, the term salivary duct carcinoma should be restricted only to those tumors histologically resembling mammary ductal carcinomas. They were originally described by Kleinsasser et al. in 1968 (2) and were included in the 2nd edition of the *WHO Classification of Salivary Gland Tumors* in 1991 (3).

Clinical features. Salivary duct carcinomas are an uncommon but not a rare tumor. More than 200 such cases have been reported (2,4–10). They account for 2% of all salivary gland tumors and 9% of all salivary gland malignancies (1). Salivary duct carcinoma has been reported to exhibit a distinct male predominance of nearly 4:1 and an age range from 22 to 91 years, with a peak incidence in the sixth and seventh decades (1,11). Most tumors arise from the parotid gland, but a few have been described in the submandibular gland and intraoral minor salivary glands as well as the sinonasal tract and larynx (1). Salivary duct carcinoma presents as a rapidly growing tumor with frequent pain and facial nerve palsy. Many salivary duct carcinomas occur *de novo*, but some develop as the malignant component of carcinoma ex pleomorphic adenoma (12).

Pathology. Grossly, most tumors are unencapsulated, highly infiltrative, and gray to white solid masses with occasional small areas of cystic change and foci of necrosis on their cut surfaces (Fig. 126). Mean tumor size is about 3.0 cm, with a range of 1.0 cm to over 6.0 cm in diameter (11).

Histologically, infiltration into adjacent salivary gland tissue and soft tissue is usually evident. The tumor bears a striking resemblance to high-grade ductal carcinoma of the breast, with a mixture of two components: intraductal and invasive (Fig. 127A). The intraductal component is described as multiple large ductal structures with a cribriform, papillary, or solid

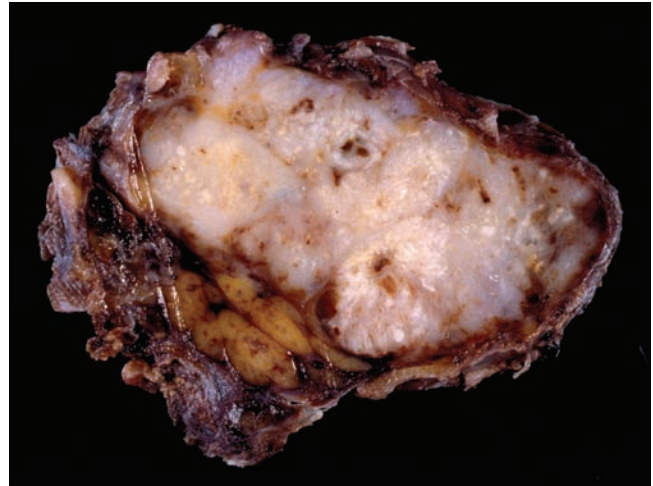


Figure 126 Salivary duct carcinoma. Cut surface of the tumor shows gray-white, solid mass with foci of necrosis.

growth pattern (Fig. 127B). However, cribriform ductal structures may also be seen in the invasive portion as well as in the metastatic foci. Cribriform carcinoma epithelium may form tumor cell arches over relatively large intercellular spaces, called “Roman-bridge” architecture. The central portion of the ductal cell nests often undergoes comedo-like necrosis. Psammoma bodies and focal squamous differentiation, some with keratinization, can be seen in the carcinoma nests.

The invasive component consists of irregular glands and cords of cells that frequently elicit a prominent desmoplastic reaction (Fig. 127C). Salivary duct carcinomas exhibiting a purely intraductal or minimally invasive form may be associated with a better prognosis. A preexisting pleomorphic adenoma component, often hyalinized, may be present in the minority of cases. It has been rarely reported that salivary duct carcinomas coexist with other specific types of salivary gland carcinoma component within the same topographical area, those being referred to as hybrid carcinomas (13). Cytologic features of the salivary duct carcinoma are characterized by large pleomorphic nuclei with coarse chromatin and prominent nucleoli (Fig. 127D). The cytoplasm is abundant and granularly eosinophilic. Mitotic figures are frequently observed in most cases. Apocrine-like metaplasia is seen when they display papillary arrangement along the dilated cystic wall. Usually, no goblet-type mucous cells are seen in the conventional salivary duct carcinoma. Both lymphovascular and perineural invasion are a frequent feature.

Immunohistochemistry. Similar to breast carcinomas, both electron microscopy and immunohistochemistry show that salivary duct carcinoma cells exhibit purely ductal cell differentiation with immunoreactivity for cytokeratin, carcinoembryonic

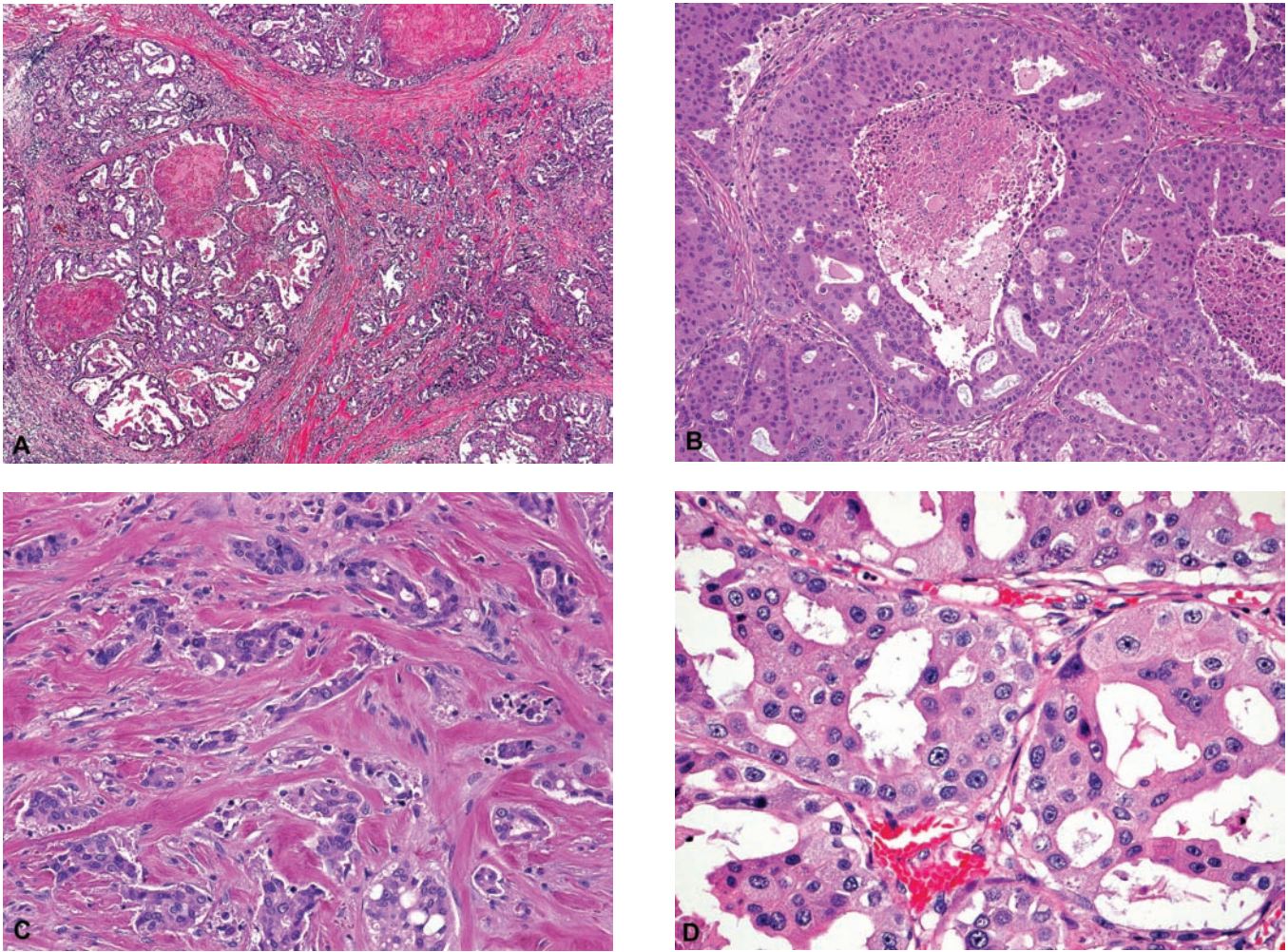


Figure 127 Salivary duct carcinoma. (A) A mixture of both intraductal and invasive growth patterns, which bears a striking resemblance to high-grade mammary ductal carcinoma of the breast. (B) Intraductal component comprised of cribriform structures with “Roman-bridge” architecture. Note that the central portion of the ductal cell nests undergoes comedo-like necrosis. (C) The invasive component consists of irregular glands and cords of cells that elicit a prominent desmoplastic reaction. (D) Carcinoma cells exhibiting large pleomorphic nuclei with coarse chromatin and prominent nucleoli. The cytoplasm is abundant and granularly eosinophilic.

antigen, epithelial membrane antigen, and gross cystic disease fluid protein-15 (5,7,14). However, unlike breast carcinomas, salivary duct carcinomas are almost always positive for androgen receptor (Fig. 128A), and negative for estrogen receptor and progesterone receptor (7,14–16). Prostate-specific antigen is detectable in some cases (16). The Ki-67 labeling index is high (average 43%) (1). Diffuse p53 immunoreactivity and mutation of p53 gene are frequent (7,10,13). Most salivary duct carcinomas show diffuse and strong membranous staining for HER-2/*neu* (Fig. 128B) with or without amplification of the gene demonstrated by fluorescence or chromogenic in situ hybridization analysis (17–20). The tumor cells themselves are negative for S-100 protein and any other myoepithelial markers. However, the myoepithelial markers, such as cytokeratin 14, smooth muscle actin, calponin, and p63, clearly highlight supportive

myoepithelial cells rimming carcinoma cell nests, confirming their intraductal nature (21).

Histologic variants. Several histologic variants of salivary duct carcinoma have already been described, including sarcomatoid (22–26), mucin-rich (27,28), and invasive micropapillary carcinomas (Fig. 55) (29). The tumor originally reported as low-grade salivary duct carcinoma has been renamed low-grade cribriform cystadenocarcinoma in the 2005 WHO classification (see the section “Cystadenocarcinoma”), because it differs from conventional salivary duct carcinoma in some of its clinical and histopathologic features, has a good prognosis, and is a purely intraductal carcinoma lesion composed of bland tumor cells (30–32). The question of a relationship between the two neoplasms remains controversial.

The sarcomatoid variant is characterized histologically by a biphasic neoplasm with both typical salivary

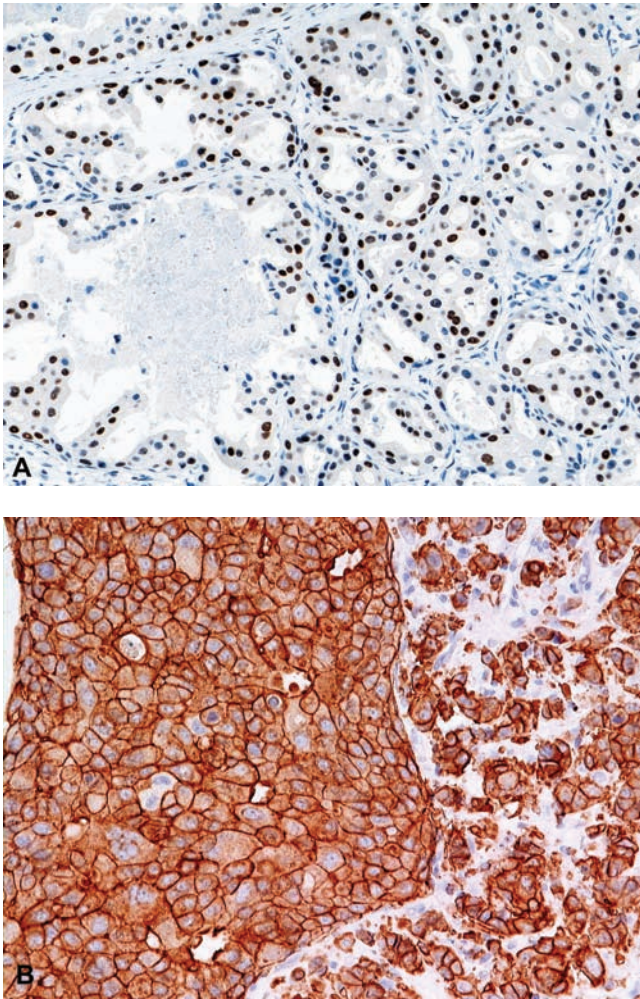


Figure 128 Salivary duct carcinoma. Immunohistochemistry. (A) Carcinoma cells are diffusely positive for androgen receptor in their nuclei. (B) Diffuse and strong membranous staining for HER-2/neu.

duct carcinoma and sarcomatoid elements (Fig. 129A) (22–26). This tumor has clinical features similar to conventional salivary duct carcinoma with a highly aggressive behavior. A transitional zone between carcinomatous and sarcomatoid elements may be present. The sarcomatoid components show various histologic features such as a fascicular pattern of spindle cells, myxoid stroma, malignant osteoid formation, and rhabdoid cells. A residual pleomorphic adenoma component is commonly identified. Generally, the carcinomatous and sarcomatoid elements are diffusely immunoreactive for cytokeratin and vimentin, respectively. However, the sarcomatoid elements also express epithelial markers, showing occasional staining for cytokeratin and consistent, focal positivity for epithelial membrane antigen. The diagnostic criteria and nomenclature for the entity “sarcomatoid salivary duct carcinoma” are controversial, especially concerning its distinction from carcinosarcoma. Although the term

“carcinosarcoma” is widely used for biphasic carcinomatous and mesenchymal neoplasms in the field of salivary gland pathology, we recommend the term “sarcomatoid variant of salivary duct carcinoma” instead of carcinosarcoma when the carcinomatous component of the lesion has histologic features fulfilling the criteria for typical salivary duct carcinoma and the term “sarcomatoid carcinoma, NOS” for lesions in which the carcinoma component is not a distinct type of salivary gland carcinoma (24).

In the mucin-rich variant of salivary duct carcinoma, the tumor is composed of mucin lakes containing islands of carcinoma cells, resembling mucinous (colloid) adenocarcinoma, in addition to the typical salivary duct carcinoma component (Fig. 55B) (27,28). The cellular and nuclear features of carcinoma cells in the mucinous component are comparable to those in the salivary duct carcinoma portion. Clinical outcome for patients with this variant appears similar to that of conventional salivary duct carcinoma.

In the invasive micropapillary variant of salivary duct carcinoma, the tumors have an invasive micropapillary architecture admixed with features typical of salivary duct carcinoma (Fig. 129C) (15). Its incidence has been reported as 17% of all salivary duct carcinomas. This is a highly aggressive variant of salivary duct carcinoma, with a propensity for extensive lymph node metastasis and rapid disease progression, similar to that noted in mammary, urothelial, ovarian, and pulmonary tumors (33). The invasive micropapillary pattern is characterized by morula-like small cell clusters without fibrovascular cores, surrounded by a clear space. Residual pleomorphic adenoma may be present. Epithelial membrane antigen-positive reaction rimming cell clusters shows a distinctive “inside-out” staining pattern (Fig. 129D).

Differential diagnosis. Although the intraductal lesions are characteristic of salivary duct carcinoma, tumors with papillary-cystic or cribriform growth patterns and/or eosinophilic cells are considered in the differential diagnosis (11). These include high-grade mucoepidermoid carcinoma, papillary-cystic variant of acinic cell carcinoma, cystadenocarcinoma, oncocytic carcinoma, and metastatic breast carcinoma.

The presence of goblet-type mucous cells as well as intermediate-type cells and the absence of a cribriform pattern distinguish high-grade mucoepidermoid carcinoma from salivary duct carcinoma. Also, high-grade mucoepidermoid carcinoma usually does not express androgen receptor. Papillary areas can superficially mimic the papillary-cystic variant of acinic cell carcinoma and cystadenocarcinoma, but the cellular atypia of these tumors is much milder than that of salivary duct carcinoma. These two low-grade tumors lack comedo-type necrosis within the tumor characteristic of salivary duct carcinoma. Additionally, diastase-resistant PAS-positive zymogen secretory granules should be present at least focally in the papillary-cystic variant of acinic cell carcinoma. Oncocytic carcinomas usually show diffuse and strong immunoreactivity for mitochondrial antigen along with positivity for phosphotungstic acid hematoxylin stain. Furthermore, this tumor typically lacks a cribriform growth pattern.

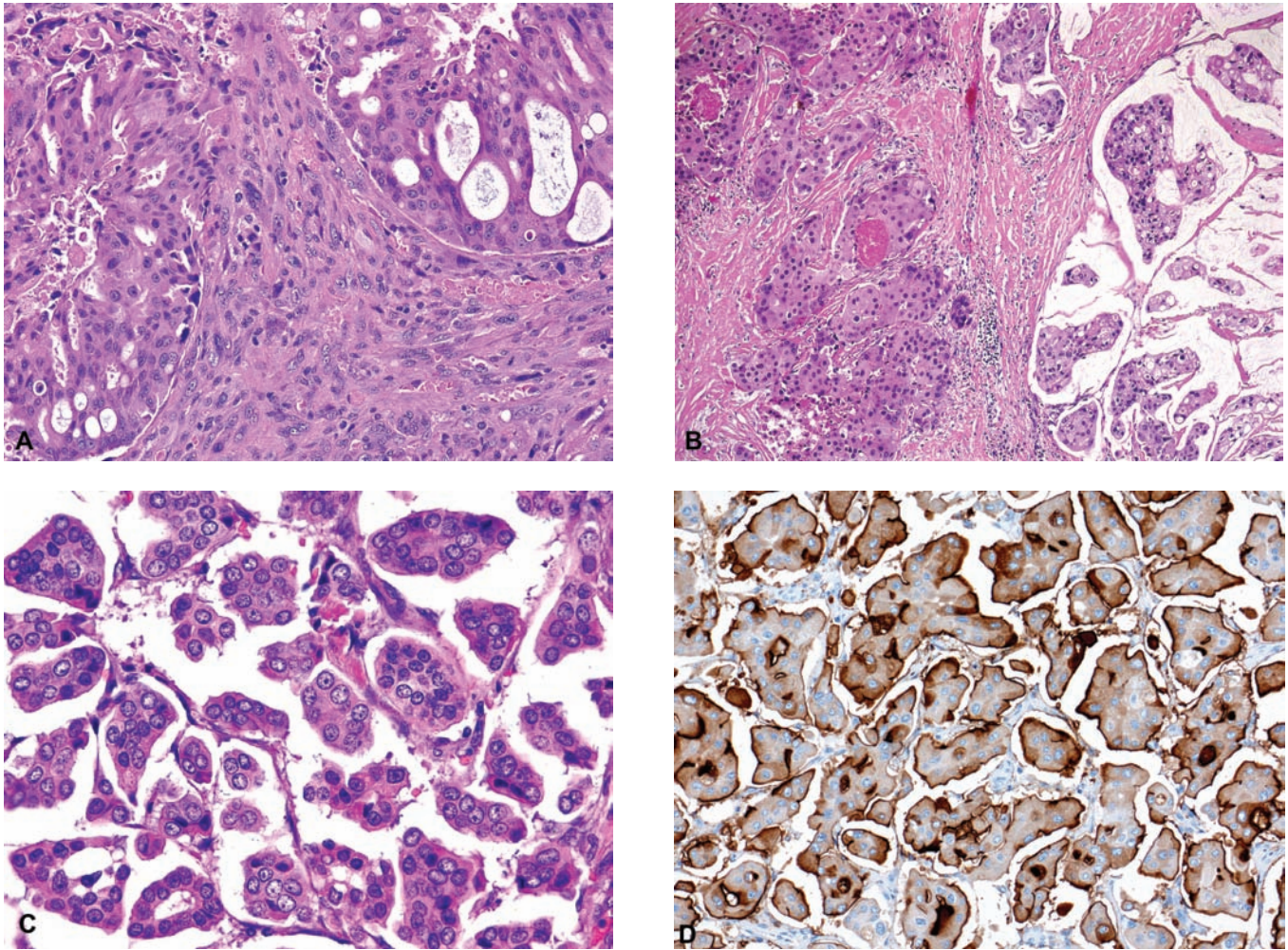


Figure 129 Histologic variants of salivary duct carcinoma. (A) Sarcomatoid variant. A biphasic neoplasm with both typical salivary duct carcinoma and sarcomatoid elements with a fascicular pattern of spindle cells. (B) Mucin-rich variant. Mucin lakes containing islands of carcinoma cells (*right*) in addition to the typical salivary duct carcinoma component (*left*). (C) Invasive micropapillary variant. Morula-like small cell clusters without fibrovascular cores, surrounded by a clear space. (D) Invasive micropapillary variant. Immunohistochemistry. Epithelial membrane antigen-positive reaction rimming cell clusters showing a distinctive “inside-out” staining pattern.

Since salivary duct carcinoma is histologically almost indistinguishable from the mammary ductal carcinoma, the possibility of primary breast carcinoma metastatic to salivary gland must be excluded. In contrast to breast cancer, salivary duct carcinoma is more common in males. The presence of the true intraductal components revealed by immunohistochemical staining for the myoepithelial markers in the salivary gland tumor suggests the primary origin. In addition, androgen receptor positive, estrogen receptor negative, and progesterone receptor negative immunophenotype favor a diagnosis of salivary duct carcinoma rather than metastatic breast carcinoma (15). However, clinical examinations to identify a breast mass are most important for accurate diagnosis.

Treatment and Prognosis. It should be emphasized that salivary duct carcinoma is one of the most aggressive malignant salivary tumors. A review of the literature confirmed that approximately 30% of the

patients with salivary duct carcinoma had local recurrence, 60% had regional lymph node metastasis, and 50% had distant metastasis (6,8,10). Sites for distant metastasis include lungs, bones, liver, brain, and skin. Of the reported patients with salivary duct carcinoma, 55% to 65% died of disease between 5 months and 10 years after diagnosis, usually within 4 years (mean survival, 29 months) (6,8,10).

The putative prognostic factors of salivary duct carcinoma include tumor size (tumors less than 3 cm in diameter having a better outcome), distant metastasis, lymph node metastasis, surgical margins, HER2/*neu* over-expression, Ki-67 labeling index, expression of estrogen receptor- β (estrogen receptor- β downregulation being associated with adverse clinical features), invasive micropapillary morphology, and proportion of intraductal component (5,7,10,17,29,34,35). The prognostic significance of the expression of p53 and DNA ploidy pattern is controversial (10,35). Treatment

usually consists of total glandectomy, accompanied by radical neck dissection and radiotherapy. Although sufficient conclusive data are lacking, anti-androgen and trastuzumab (Herceptin) might provide hope for systemic therapy for patients with advanced stage salivary duct carcinoma (36,37).

Adenocarcinoma, Not Otherwise Specified

Introduction. Adenocarcinoma, not otherwise specified (NOS), is defined as "a malignant salivary gland tumor that exhibits ductal differentiation but lacks any of the histomorphologic features that characterize the other defined types of salivary carcinoma" (1). Although many salivary gland carcinomas originate from the salivary duct unit and generically belong to the large category of "adenocarcinoma," the modifying term "NOS" is only applied to those tumors that lack sufficient histologic features of the specific categories of salivary gland carcinoma (1).

Various types of adenocarcinomas have been recognized and separated from the adenocarcinoma NOS group since the 1st edition of the *WHO Classification of Salivary Gland Tumors* appeared in 1972 (2). Accordingly, the second edition of the WHO classification published in 1991 significantly increased the numbers of the tumor entities (3). In particular, the recognition of polymorphous low-grade adenocarcinoma, salivary duct carcinoma, epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, and papillary cystadenocarcinoma have probably greatly contributed to the decrease in the number of cases included in adenocarcinoma NOS group (4-8). However, according to the AFIP series, for example, adenocarcinoma NOS still constitutes a considerable proportion, being only the second most common type of all salivary gland malignancies next to mucoepidermoid carcinoma (9). Because the 2005 WHO classification added only three relatively rare tumor entities, namely, clear cell carcinoma NOS, low-grade cribriform cystadenocarcinoma, and sialoblastoma, it seems likely that the frequency of adenocarcinoma NOS has not been substantially decreased after the recognition of the scheme (1).

In 2004, Ghannoum and Freedman introduced a new type of salivary gland carcinoma they called "signet-ring cell (mucin-producing) adenocarcinoma of minor salivary glands," and distinguished it from the adenocarcinoma NOS group (10). This tumor entity is not included in the 2005 *WHO Classification of the Salivary Gland Tumors*; thus it will be briefly described later in this section.

Clinical features. The incidence of adenocarcinoma NOS is variable in several major series (5-9,11-14). Based on recent series data, adenocarcinoma NOS represents an uncommon, but not rare, salivary gland malignancy, accounting for approximately 3% to 9% of all salivary gland tumors and 8% to 17% of all salivary gland carcinomas (5-9,14). Age ranges from 10 to 93 years, with a peak incidence in the sixth and seventh decades. Reported gender differences of adenocarcinoma NOS are inconsistent. The AFIP files show these tumors to have a slight female

predominance (9). The major salivary glands, mostly the parotid gland, are more frequently affected than the minor salivary glands. Patients with adenocarcinoma NOS usually present with a solitary painless mass, but approximately 20% of the patients with parotid tumors complain of pain or facial nerve weakness, and nearly half of the tumors are fixed to the skin or deep tissues (11). Palatal tumors may ulcerate and involve the underlying bone.

Pathology. Grossly, the tumor shows ill-defined infiltrative borders, but it may be focally circumscribed. The cut surface is mostly tan to gray-white, and the tumor forms a solid mass, often with foci of hemorrhage or necrosis.

Histologically, the tumors are characterized by variable glandular or duct-like structures and invasion into the adjacent salivary gland parenchyma and sometimes surrounding connective tissue, as well as muscle or bone. Apart from the glandular structures, adenocarcinoma NOS exhibits a variety of architectural patterns, including solid sheets, papillary, cystic, cribriform, cords, lobular, and trabecular (Fig. 130). A mixture of several architectural growth patterns is common, but one architectural pattern may predominate. Diverse tumor-cell types can be seen in adenocarcinoma NOS. In most tumors, cuboidal-, oval-, or polygonal-cell type dominates, but scattered oncocytoïd-, clear-, melanoma-like-, mucinous-, or sebaceous-cell types may occasionally be present. Tumor necrosis and perineural and vascular invasion are common. By definition, adenocarcinomas NOS lack the characteristic histologic features of other recognized salivary adenocarcinomas, but limited foci that resemble specific tumor entities, such as adenoid cystic carcinoma, acinic cell carcinoma, epithelial-myoepithelial carcinoma, cystadenocarcinoma, or salivary duct carcinoma, may be seen and the presence of these features does not preclude a diagnosis of adenocarcinoma NOS.

Generally, the histologic grading system of low, intermediate, and high is applied to adenocarcinoma NOS and is based on differentiation or degree of gland formation, cytologic atypia, mitotic count, and tumor necrosis (Fig. 130) (11,13). Gland formation tends to be prominent in low-grade tumors but not in high-grade tumors, but the extent of gland formation alone may not be enough for the assessment of the grade of adenocarcinoma NOS. It has been proposed that high-grade tumors should be distinguished from low-grade tumors by the presence of one or more of the following features: nuclear atypia, high mitotic rate, atypical mitotic figures, necrosis, perineural invasion, bony invasion, angiolymphatic invasion, or aggressive invasion pattern. An aggressive pattern of invasion is seen as infiltration at the tumor interface composed of small islands or strands, or 1 mm or more of normal tissue between tumor islands (8). Most adenocarcinomas NOS are considered to be high-grade histologically.

Immunohistochemically, the tumor cells are usually positive for pan-cytokeratin and negative for S-100 protein, smooth muscle actin, and calponin.

Differential diagnosis. The diagnosis of adenocarcinoma NOS is essentially based on the exclusion

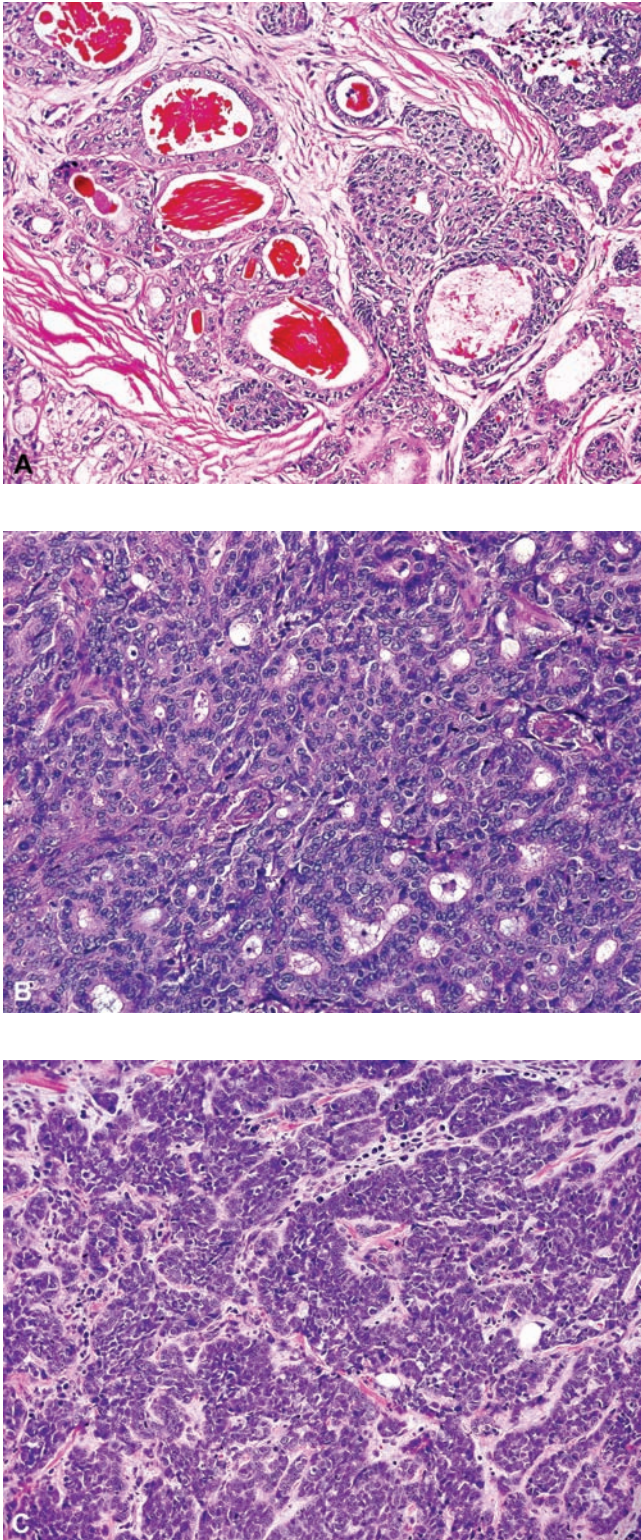


Figure 130 Adenocarcinoma, not otherwise specified. (A) Low-grade tumor. Prominent well-formed glandular formations. (B) Intermediate-grade tumor. Fused glandular formations with focal solid areas. (C) High-grade tumor. Irregularly shaped islands and strands of anaplastic carcinoma cells. Glandular formations are inconspicuous in this figure.

of specific types of all gland-forming carcinomas occurring in the salivary glands. Selected possible differential diagnoses include polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, cystadenocarcinoma, salivary duct carcinoma, and metastatic adenocarcinomas.

Polymorphous low-grade adenocarcinoma and low-grade adenocarcinoma NOS share bland nuclear morphology and numerous ductal and tubular structures. However, polymorphous low-grade adenocarcinoma shows a mixture of other features, such as solid, fascicular, and cribriform patterns as well as a concentric, targetoid appearance. Adenocarcinomas NOS lack the biphasic pattern of duct-lining and myoepithelial cells characteristic of epithelial-myoepithelial carcinoma. The extensive papillary and cystic architecture of cystadenocarcinoma is not the feature of adenocarcinoma NOS. The presence of an “intraductal” cribriform growth pattern of large pleomorphic eosinophilic cells resembling mammary ductal carcinoma leads to a diagnosis of salivary duct carcinoma rather than high-grade adenocarcinoma NOS. The possibility of metastatic adenocarcinomas should be ruled out before the diagnosis of adenocarcinoma NOS is made, based on the clinical information and, where appropriate, immunohistochemical profile. However, interpretation should be cautious, as immunoreactivity for prostate-specific antigen in adenocarcinoma NOS has been reported.

Treatment and prognosis. Because of the differences of classification schemes in various series, reliable data on the biologic behavior of adenocarcinoma NOS are sparse (11,13,14). Clinical stage, histologic grade, and the site of involvement appear to be the major prognostic factors (11,13). Generally, adenocarcinoma NOS is a high-grade lesion with an aggressive clinical behavior (11,13). According to the data of the largest series (11), even if the reported patients comprise a possible case mixture of “true” adenocarcinoma NOS and specific adenocarcinoma entities, the frequency of local recurrence, cervical lymph nodal metastases, and distant metastases were 51%, 27%, and 26% of the patients, respectively (11). Overall cure rates at 5, 10, and 15 years were 41%, 34%, and 28%, respectively. Regarding the clinical stage, the 15-year cure rates for stages I, II, and III tumors are 67%, 35%, and 8%, respectively. Histologic grade is also strongly correlated with survival; the 15-year cure rates for low-, intermediate-, and high-grade tumors are 54%, 31%, and 3%, respectively. Survival was also dependent on tumor site; tumors involving the oral cavity had a more favorable prognosis than those of the parotid or submandibular glands. The treatment of choice is complete surgical excision. Additionally, higher-stage or higher-grade tumors require wide surgical excision with neck dissection and adjuvant radiation therapy.

Signet-Ring Cell (Mucin-Producing) Adenocarcinoma of Minor Salivary Gland. Only one series consisting of seven cases has been reported (10). The tumor occurred in adults, ranging in age from 32 to 72 years with a mean age of 56.4 years (two men, five women). All cases developed in the minor salivary glands of

the oral cavity. The patients presented with an asymptomatic mass and neither bone invasion nor cervical lymph node or distant metastases after excision was found.

Histologically, the tumor is unencapsulated and infiltrates into the adjacent minor salivary gland tissue. It lies close to the overlying mucosal epithelium, which may show pseudoepitheliomatous hyperplasia. Variable growth patterns, including narrow parallel strands, interconnecting cords, small nests, microcystic, or individually infiltrating cells, are seen in the tumor. A few duct-like structures may also be seen. The tumor is predominantly composed of signet-ring cells with intracytoplasmic mucin and eccentric, indented nuclei. Signet-ring cells mingle with minor populations of polygonal cells with eosinophilic or clear cytoplasm. Generally, nuclear atypia is absent and mitotic figures are rare, but focal nuclear pleomorphism and occasional mitoses can be present. Unlike mucinous adenocarcinoma, pools of extracellular mucin are an uncommon finding and if present are limited. Perineural invasion may be observed, but vascular invasion is infrequent.

Myoepithelial Carcinoma

Introduction. Myoepithelial carcinoma, also referred to as malignant myoepithelioma, is a rare salivary gland tumor, which is the malignant counterpart of myoepithelioma. The entity was first described by Stromeyer et al. in 1975 (1) and was added to the 2nd edition of the *WHO Classification of Salivary Gland Tumors* (2). Myoepithelial carcinoma is defined as "a neoplasm composed almost exclusively of tumor cells with myoepithelial differentiation, characterized by infiltrative growth and potential for metastasis" (3,4). However, the determination of the myoepithelial nature of the neoplasm may be difficult by light microscopy alone because of the wide variety of histologic as well as cellular features of the tumor cells. A combination of histomorphologic, immunohistochemical, and ultrastructural criteria is often required to delineate myoepithelial differentiation of the tumor cells. Therefore, this tumor may have been misdiagnosed as various other salivary gland entities in the past, such as the broader category of "malignant mixed tumor" (5).

Clinical features. Myoepithelial carcinoma is considered extremely rare, but it may be more common than previously thought (5). Approximately 90 cases of myoepithelial carcinoma have been reported (1,5–14). It accounts for less than 0.4% of all salivary gland tumors. The age range is from 14 to 86 years, and the mean age of 55 years is about 10 years older than that of myoepithelioma, and no gender predilection is noted (3). Myoepithelial carcinoma arises preferentially in the parotid gland (75%), but it also occurs in the minor salivary glands (25%), especially the palate, and submandibular gland (10%) (3). The maxillary sinus, larynx, and bronchus have been rarely reported as the primary site of this neoplasm (15). Most patients present with a chief complaint of a painless mass. Myoepithelial carcinomas may arise *de novo*, but a half or more may develop via

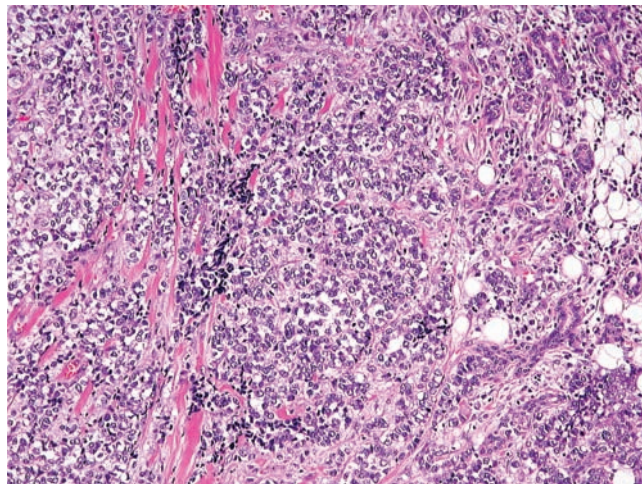


Figure 131 Myoepithelial carcinoma. Carcinoma irregularly invades into the surrounding salivary gland.

evolution from a preexisting pleomorphic adenoma or myoepithelioma (5,7,11).

Pathology. Macroscopically, the cut surface of the tumor typically shows an unencapsulated, gray-white solid mass with nodules. A gelatinous appearance is common and yellow foci of necrosis and cystic degeneration may be seen. The size of the tumor varies and it ranges from 2 to 20 cm in greatest dimension with a mean of 3.5 cm (5).

Histologically, the tumor invades into the surrounding normal salivary gland (Fig. 131), or adjacent adipose or muscular tissue; the extent of invasion varying according to case. A multinodular outline with tongue-like pushing margins is a common type of invasion in this tumor. The multinodular architecture consists of solid, sheet-like, trabecular, reticular, and lace-like growth patterns of tumor cells

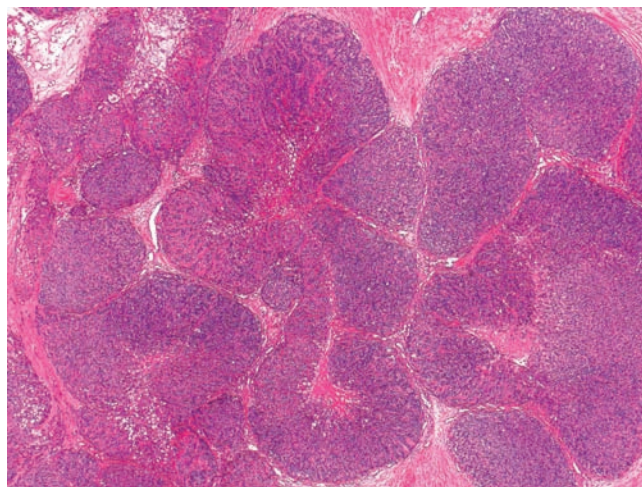


Figure 132 Myoepithelial carcinoma. Low-power view showing multinodular architecture.

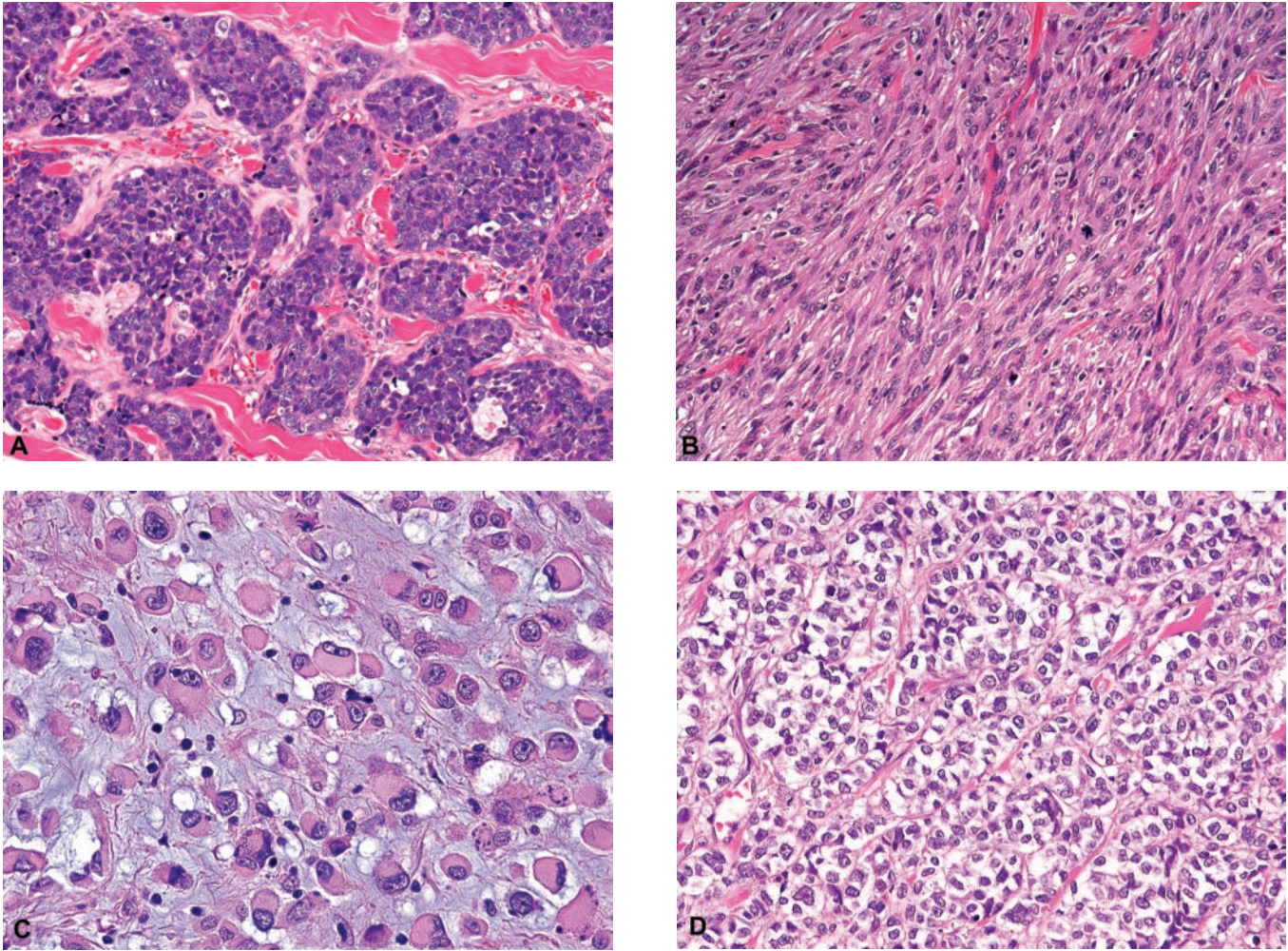


Figure 133 Myoepithelial carcinoma. (A) Epithelioid cell type. The epithelioid cells forming solid nests, cords, or trabeculae in a hyalinized stroma. (B) Spindle cell type. The spindle cells arranged in a vaguely interlacing fascicular pattern. (C) Plasmacytoid cell type. The plasmacytoid cells exhibiting eccentrically located nuclei and abundant cytoplasm in a myxoid background. (D) Clear cell type. Solid nests of epithelioid type carcinoma cells with clear cytoplasm.

intermixing with variable amounts of myxoid or hyaline material (Fig. 132). The center of the tumor cell nests often undergoes necrosis or paucicellular myxoid degeneration, sometimes creating a pseudocystic appearance. It is unclear whether a tumor exhibiting predominantly myoepithelial differentiation with focal ductal differentiation can be diagnosed as myoepithelial carcinoma or should be considered in the category of epithelial-myoepithelial carcinoma. In addition, recent reports have broadened the histomorphologic spectrum of epithelial-myoepithelial carcinoma (16). Although very limited foci of ductal differentiation may not preclude the diagnosis of myoepithelial carcinoma (4), in order to avoid confusion, we propose that any true ductal structures should not be present in this tumor.

As in myoepithelioma, the tumor cells in myoepithelial carcinoma show wide morphologic variation, consisting of epithelioid, spindle, plasmacytoid and clear cell subtypes (Fig. 133). Although epithelioid cell

is the most common cell type, a mixture of several cell types within a tumor is frequently seen. The epithelioid cells are polygonal, with central nuclei, coarse chromatin and prominent nucleoli (Fig. 133A). These cells may be arranged in patternless sheets, cords, or trabeculae in hyalinized stroma. Loose clusters in a myxoid background with pseudoglandular structures forming cleft-like spaces can also be observed. The spindle cells have centrally located nuclei and are sometimes arranged in a vaguely interlacing fascicular pattern (Fig. 133B). The plasmacytoid cells have eccentrically located nuclei and abundant cytoplasm, superficially mimicking plasma cells (Fig. 133C). Clear cytoplasm, because of accumulation of granular PAS-positive glycogen, is usually seen in the epithelioid type cells (Fig. 133D) (10,14). The clear-cell type may resemble a vacuolated signet-ring cell or lipoblast-like cell (5). Sometimes, cells of intermediate appearance are present among the cells of different types. Small foci of squamous differentiation with or

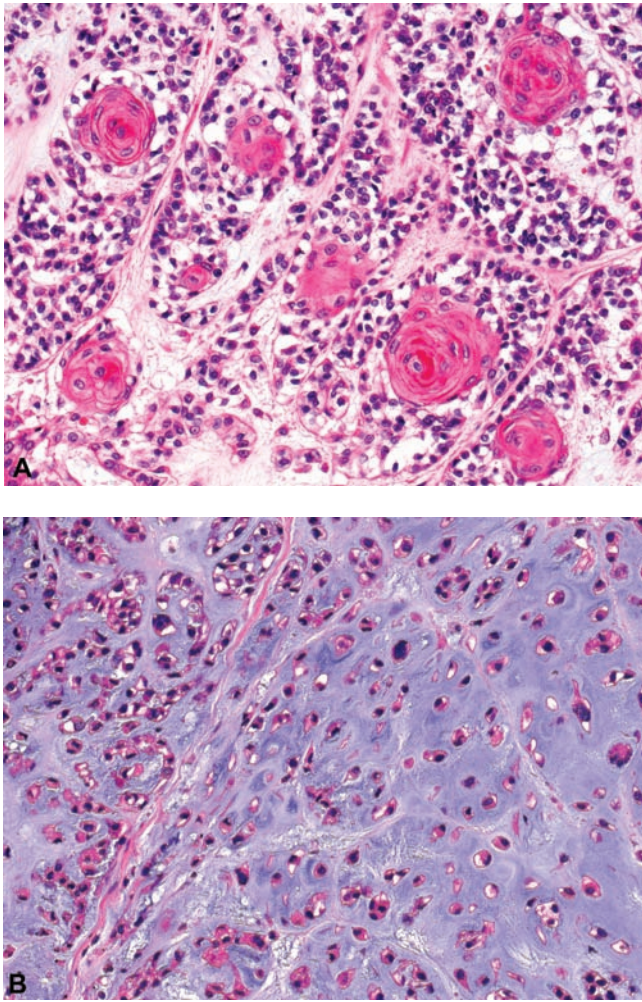


Figure 134 Myoepithelial carcinoma. (A) Several foci of squamous differentiation with keratinization. (B) Chondroid differentiation.

without keratinization as well as chondroid features may be seen (Fig. 134). Cellular pleomorphism varies from mild to severe. In rare cases, the cytologic features are virtually indistinguishable from those of myoepithelioma. On the other hand, tumor exhibiting marked cellular pleomorphism with cells showing giant and bizarre nuclei is occasionally observed. Mitotic figures are easily identified and are sometimes frequent. Perineural or vascular invasion is present in 44% and 16%, respectively (5). A preexisting pleomorphic adenoma or myoepithelioma component is commonly seen. In addition, a case of dedifferentiation to undifferentiated carcinoma from histologically low-grade myoepithelial carcinoma has been reported (17).

Ultrastructurally, tumor cells contain microfilaments with or without focal densities in their cytoplasm and have frequent desmosome-like junctions (Fig. 135) (5,11). Abundant glycogen deposits are evident in the clear-cell type (5). A basal lamina may be focally present.

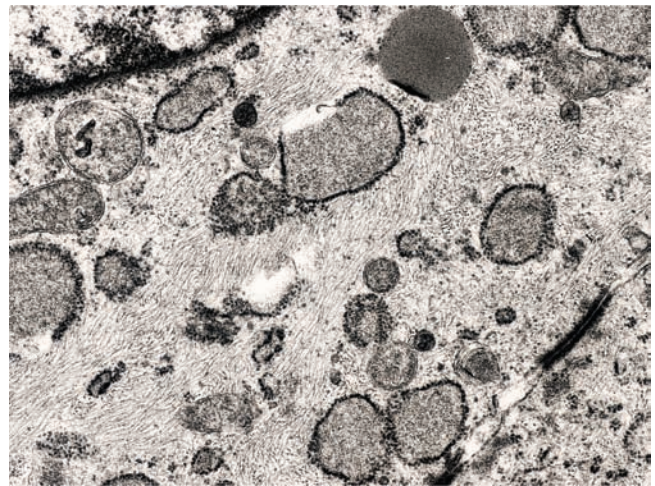


Figure 135 Myoepithelial carcinoma. Electron micrograph of the carcinoma cell showing abundant microfilaments and desmosome-like junctions.

Immunohistochemistry. The immunohistochemical characteristics of myoepithelial carcinoma indicate that these tumors are composed of modified neoplastic myoepithelial cells showing various stages of differentiation (5,7,9,11). Myoepithelial carcinomas are almost always positive for pan-cytokeratin, S-100 protein, vimentin, and p63. The tumor cells are variably immunoreactive for calponin (75–100%), smooth muscle actin (50–80%), cytokeratin 14 (53–80%), caldesmon (50%), muscle-specific actin (31–70%), glial fibrillary acidic protein (31–50%), smooth muscle myosin heavy chain (30%), and epithelial membrane antigen (20–100%) (5,11). Positivity for pan-cytokeratin, together with one or more myoepithelial markers, is required for the diagnosis of myoepithelial carcinoma. Tumors do not stain with carcinoembryonic antigen, HMB45, or desmin.

Differential diagnosis. Because of the diverse histologic features of myoepithelial carcinoma, a variety of neoplasms must be included in the differential diagnosis. These include myoepithelioma, various types of sarcoma such as leiomyosarcoma, malignant fibrous histiocytoma, malignant nerve sheath tumor, and synovial sarcoma, plasmacytoma, and melanoma.

Myoepithelial carcinoma is principally distinguished from myoepithelioma by several histologic features such as invasive growth (being the most important hallmark), necrosis, cellular pleomorphism, and mitosis. Assessment of cell proliferative activity is helpful in the differential diagnosis between myoepithelioma and myoepithelial carcinoma, and more than 7 mitotic figures/10 HPFs or a Ki-67 labeling index over 10% is diagnostic for myoepithelial carcinoma (11). Malignant nerve sheath tumor and melanoma express S-100 protein, but unlike myoepithelial carcinomas, all sarcomas, plasmacytoma, and melanoma are negative for cytokeratin and specific myoepithelial markers such as calponin and smooth muscle actin.

The clear cell variant of myoepithelial carcinoma should be distinguished from various types of salivary gland tumors with predominant clear cell morphology, including epithelial-myoepithelial carcinoma, clear cell carcinoma (NOS), mucoepidermoid carcinoma, oncocytoma, acinic cell carcinoma, sebaceous carcinoma, and metastatic renal cell carcinoma (see the section "Clear Cell Carcinoma, NOS") (10,18,19). The distinction between myoepithelial carcinoma and epithelial-myoepithelial carcinoma is based on the presence or absence of the true ductal formation.

Treatment and prognosis. The clinical behavior of myoepithelial carcinoma varies, but it is generally considered to be of intermediate- to high-grade malignancy (5,7,11). Approximately, one third of the patients die of the disease, usually with distant metastases, another third develop recurrences but do not die of disease, and the remaining third are free of disease (4). Common sites for metastasis include the cervical lymph nodes and distant organs, such as the lungs, liver, bones, kidney, and brain (5,11).

Myoepithelial carcinomas exhibiting high proliferative activity assessed by mitotic count and/or Ki-67 labeling index, histologic aggressiveness such as perineural permeation and extensive invasion into the surrounding tissue, and marked cellular pleomorphism have a poor prognosis (11). p53 over-expression suggests an unfavorable course (11). DNA content and S-phase fraction of tumor cells are good predictors of aggressive biologic behavior (20). There is no difference in outcome with regard to the presence or absence of preexisting pleomorphic adenoma or myoepithelioma (5,11). No correlation between nucleolar organizer regions (an indicator of cell proliferative activity) and clinical outcome has been reported (21). There is no apparent association between the cell type and clinical behavior of myoepithelial carcinoma (5,11).

Complete wide surgical excision is the recommended treatment for myoepithelial carcinoma. The effectiveness of chemotherapy or radiation therapy, or both, for this tumor remains unknown.

Carcinoma Ex Pleomorphic Adenoma

Introduction. Carcinoma ex pleomorphic adenoma has been defined as "a pleomorphic adenoma from which an epithelial malignancy is derived" (1). Synonyms include carcinoma arising in a benign mixed tumor, carcinoma ex benign mixed tumor, carcinoma arising in pleomorphic adenoma, and malignant mixed tumor. In the past, the term malignant mixed tumor has also included carcinosarcoma and metastasizing pleomorphic adenoma. This is a particularly unhelpful name as these tumors are now regarded as independent entities.

Clinical features. Carcinoma ex pleomorphic adenoma forms the large majority of malignant tumors associated with pleomorphic adenoma (>95%) (2–4). In a major review of the literature, carcinoma ex pleomorphic adenoma accounted for approximately 3.6% of all salivary tumors (range, 0.9–14%), 12% of all salivary malignancies (range,

2.8–42.4%), and 6.2% of all pleomorphic adenomas (range, 1.9–23.3%) (2). It is probable that the true incidence of carcinoma ex pleomorphic adenoma is higher because the malignant component may overgrow and efface the original pleomorphic adenoma masking the origin of the tumor (4). The parotid gland is the most frequent major gland site (82%) but tumors may also develop in the submandibular gland (18%) and very rarely the sublingual gland (0.3%) (2). In the minor salivary glands, about 60% of carcinoma ex pleomorphic adenoma involve the palate with lesser numbers forming in the lips, tongue, buccal mucosa, and tonsil (5). There is a wide overall age distribution but tumors rarely present before the age of 20 and most cases are seen in the sixth or seventh decades of life. This is approximately a decade later than in patients with benign pleomorphic adenomas. The typical history is a rapid increase in size of a mass that has been present for many years. However, occasionally the initial presentation may be a rapidly enlarging tumor with no history of a preexisting mass (2,6). The risk of malignant transformation in pleomorphic adenoma appears to increase progressively with time (7). However, a significant proportion of patients, particularly those in the younger age groups, have a clinical history of less than three years (2,8). Carcinoma ex pleomorphic adenoma usually forms a painless mass but pain, nerve palsy, and skin fixation or ulceration may be seen in progressive disease. Regional metastases are common at presentation and the tumor often becomes more widely disseminated (9).

Pathology. The size of carcinoma ex pleomorphic adenoma ranges from 1.5 to 25 cm in greatest diameter (4,10). On average, this is twice the size of benign pleomorphic adenomas. Large or densely hyalinized tumors and the presence of necrosis, hemorrhage, or cystic degeneration should raise the suspicion of malignancy and such tumors may require extensive sampling. Grossly, carcinoma ex pleomorphic adenomas are usually poorly circumscribed and many are extensively infiltrative. Occasional tumors resemble their benign counterpart and are well circumscribed or completely encapsulated (10,11). Sometimes the preexisting pleomorphic adenoma is represented by no more than an area of scarring. About 40% of carcinoma ex pleomorphic adenomas show macroscopic evidence of facial nerve involvement (9).

The most common malignant component is a poorly differentiated adenocarcinoma (NOS) or salivary duct carcinoma (Figs. 136,137). Other malignant elements include mucoepidermoid, polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma, clear cell or myoepithelial carcinoma (9,12). In addition, carcinoma ex pleomorphic adenoma can show multiple distinct carcinoma types in the same tumor mass. Occasionally, no histologically benign remnant can be found. If there is extensive scarring or calcification or if there is evidence of a previously excised pleomorphic adenoma at that site, a diagnosis of carcinoma ex pleomorphic adenoma is probable. Some consider the history of a long-standing mass in

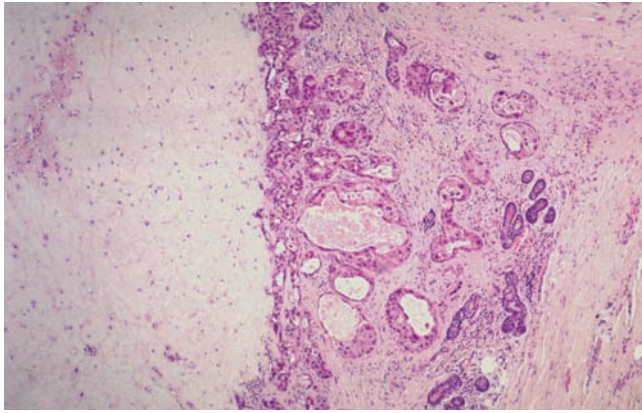


Figure 136 Carcinoma ex pleomorphic adenoma showing adenocarcinoma developing next to cartilaginous area.

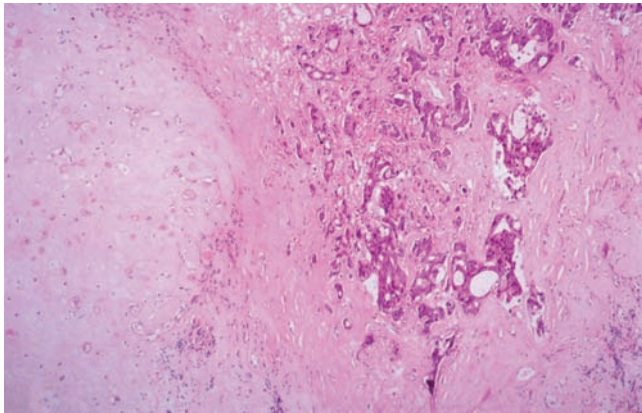


Figure 137 Carcinoma ex pleomorphic adenoma showing poorly differentiated carcinoma developing next to cartilaginous area.

these circumstances is insufficient to justify a diagnosis of carcinoma ex pleomorphic adenoma (9). The most reliable criterion for the diagnosis of carcinoma ex pleomorphic adenoma is an infiltrative, destructive growth pattern (Fig. 138). Nuclear hyperchromasia and pleomorphism are frequent, although occasional tumors may show minimal cytologic atypia. The tumor grade shows a positive correlation with prognosis. Necrosis is a common feature and mitoses may be frequent. Carcinoma ex pleomorphic adenomas can be subclassified into noninvasive, minimally invasive (≤ 1.5 mm penetration of the malignant component into extracapsular tissue) and invasive (> 1.5 mm of invasion). The first two groups appear to have an excellent prognosis (11) but the outlook is much poorer in the latter group.

Some pleomorphic adenomas have foci of cells showing variable degrees of dysplasia but confined within the main tumor mass. These tumors have been given a variety of names including intracapsular

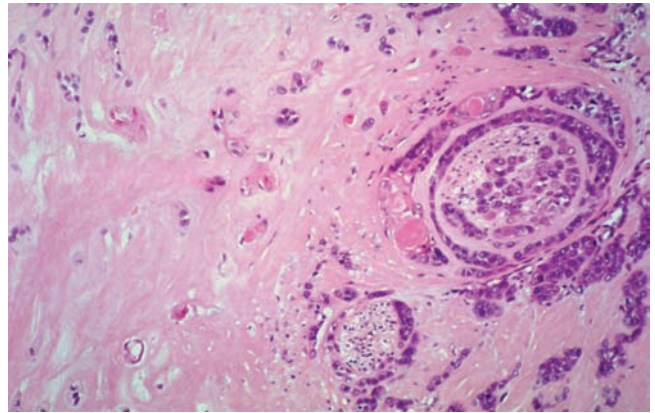


Figure 138 Perineural invasion next to remnant of scarred pleomorphic adenoma.

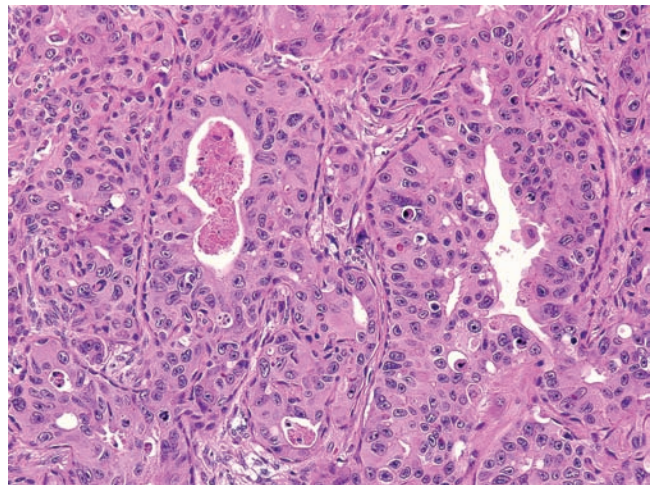


Figure 139 Noninvasive carcinoma ex pleomorphic adenoma showing dysplastic cells replacing the inner duct layer leaving a benign myoepithelial layer.

carcinoma, dysplastic pleomorphic adenoma, and carcinoma in situ in pleomorphic adenoma. None of these terms is entirely satisfactory and the preferred designation is noninvasive carcinoma ex pleomorphic adenoma. Atypical changes may be focal or diffuse and multifocal dysplastic elements may overgrow and replace much of the benign tumor. In the early stages, tumor cells replace the normal inner duct epithelial layer, leaving the normal peripherally located myoepithelial layer intact (Figs. 139,140). It has been postulated that this represents intraductal carcinoma (13) and this has been associated with genetic and morphologic evidence of dysfunctional p53 (14). If there is any evidence of destructive invasion through the capsule into peritumoral tissues, the tumor is regarded as a noninvasive carcinoma ex pleomorphic adenoma.

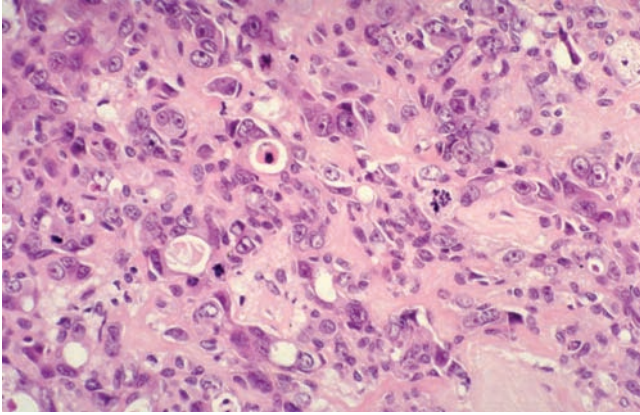


Figure 140 Noninvasive carcinoma ex pleomorphic adenoma showing more extensive dysplastic change.

Differential diagnosis. An important differential diagnosis for carcinoma ex pleomorphic adenoma is from tumors showing areas of extensive areas of hyalinization such as adenoid cystic carcinoma, salivary duct carcinoma, and polymorphous low-grade adenocarcinoma. Finding remnants of pleomorphic adenoma with myxoid, chondroid, or bland ductal/myoepithelial components should allow appropriate classification of carcinoma ex pleomorphic adenoma. Carcinomas may rarely arise in a histologically benign adenoma (monomorphic adenoma) and these must be differentiated from carcinoma ex pleomorphic adenoma because they appear to have a more favorable prognosis (15). Tumors showing several distinctive malignant components need to be distinguished from hybrid tumors by identifying remnants of pre-existing pleomorphic adenoma. The most important differential diagnosis, however, is between non- and minimally invasive carcinoma ex pleomorphic adenoma and the more typical invasive carcinoma ex pleomorphic adenoma, as this has important therapeutic and prognostic significance. It affects decisions regarding neck dissections and the use of adjuvant radiotherapy. In this respect, HER-2/*neu* amplification has been reported in focal dysplastic cells in noninvasive carcinoma ex pleomorphic adenoma but not in the surrounding maternal pleomorphic adenoma (16). In addition, foci of noninvasive carcinoma ex pleomorphic adenoma showed a higher MIB1 proliferative index when compared with the surrounding pleomorphic adenoma.

Molecular-genetic data. Deletions of chromosome 5(q22-23, q32-33) and t(10;12) (p15;q14-15) have been reported. There is a breakpoint of the high mobility group protein HMGIC and translocations to the 10 marker protein have resulted in deletions/amplifications of segments containing both HMGIC and MDM2 genes (1). Abnormalities in chromosome 8 are the most commonly encountered aberration in both pleomorphic adenoma and carcinoma ex pleomorphic adenoma, and this probably indicates an early event in the genesis of these tumors.

Rearrangements of 8q12 are the most frequent finding, and alterations at 12q13-15 with amplifications of HMGIC and MDM2 genes have been described (17). These findings suggest that amplification and over-expression of HMGIC and possibly MDM2 might be important genetic events in the malignant transformation of pleomorphic adenomas (18,19). Microsatellite analysis has shown that loss of heterozygosity (LOH) is common on chromosome 8q and 12q in both pleomorphic adenoma and carcinoma ex pleomorphic adenoma, suggesting the presence of one or more tumor suppressor genes at these locations (19,20). LOH at chromosome 17p has been reported in carcinoma ex pleomorphic adenoma. In addition, chromosome 17p alterations have been correlated with an increased proliferative rate and a high disease stage (19). It has therefore been proposed that changes in 8q and/or 12q are early events in the progression of pleomorphic adenoma to carcinoma ex pleomorphic adenoma and that LOH at 12q might identify a subset of pleomorphic adenomas that is more likely to undergo metastasis (20). LOH at 17q may be a separate event that precedes malignant transformation and progression. These late events may relate to loss or mutation of p53, which resides on 17p, and P53 over-expression has been reported in noninvasive carcinoma ex pleomorphic adenoma (21). Another study concluded that p53 and c-erbB1 proteins were involved in the early stages of malignant transformation of pleomorphic adenoma (22). Homozygous deletion of p16 on chromosome 9q21 has also been reported in the malignant but not the benign component of one of four cases of carcinoma ex pleomorphic adenoma (23). Microsatellite instability was found in the malignant elements of 2 cases and in one case it was detected in the benign component, suggesting premalignant genetic instability.

Treatment and prognosis. The treatment of choice for carcinoma ex pleomorphic adenoma is radical local excision. Locoregional lymph node dissection and adjuvant radiation therapy is recommended for widely invasive tumors. If the carcinomatous component is cytologically low grade or minimally invasive and the tumor appears to have been completely excised, then adjuvant radiation therapy may not be necessary.

It appears that patients with noninvasive or minimally invasive carcinoma ex pleomorphic adenoma have a prognosis similar to that of benign pleomorphic adenoma (9). There is only one report of a noninvasive carcinoma ex pleomorphic adenoma leading to a regional lymph node metastasis (24). Invasive carcinomas ex pleomorphic adenomas, however, are usually high-grade and are associated with a poor prognosis. About 40% to 50% of patients develop one or more recurrences (2,4,7,9). As many as 70% of patients develop local or distant metastases (6). The sites of metastatic spread, in order of frequency, are lung, bone (especially spine), abdomen, and central nervous system (4,25). Carcinoma ex pleomorphic adenoma with capsular penetration of more than 1.5 mm is associated with a poor prognosis; survival rates at 5, 10, 15, and 20 years range from 25% to 65%, 18% to 50%, 10% to 35%, and 0% to 38%, respectively

(4,6,7,9,10,25). It is important, therefore, to identify carcinomas ex pleomorphic adenoma that are intracapsular and those invading through the capsule as noninvasive or invasive, respectively, and to separate within the latter group minimally and widely invasive tumors.

Several other studies have shown that depth of invasion is an important indicator of prognosis. However, the depth chosen varies widely in different studies making interpretation of the data problematical. One study found that no patients with less than 8 mm invasion from the capsule died from the tumor, whereas all patients with invasion greater than 8 mm beyond the capsule ultimately died of disease (10). The local recurrence rate in this series also correlated with extent of invasion. There was a local recurrence rate of 70.5% in tumors with invasion beyond 6 mm from the capsule, as compared with 16.6% for tumors with invasion of less than 6 mm. Another study showed that of four patients with carcinoma ex pleomorphic adenoma invading 5 mm beyond the capsule, two died of the disease. Two patients with invasion less than 5 mm had no tumor progression (9). The improved prognosis for minimally invasive tumors (≤ 1.5 mm) has been shown by eight patients having recurrence-free periods ranging from 1 to 4 years (mean, 2.5 years) (11). Further studies using larger numbers of patients and more exact histologic criteria are necessary to establish more clearly the relationship between depth of invasion and prognosis.

The reported effect of tumor size on prognosis has also been variable. Some studies have shown a poorer prognosis in larger tumors (3,9) whereas others could find no significant relationship between size and survival (7,10). Lewis et al. (9) could find no correlation with tumor subtype, unlike Tortoledo et al. (10) who reported a correlation between the subtype of the carcinomatous component and the five-year survival rates. In their study there was a 30% survival rate for undifferentiated carcinomas, 50% for myoepithelial carcinomas, 62% for adenocarcinomas (NOS), and 96% for polymorphous low-grade adenocarcinomas (10). Additional factors reported to be of prognostic significance have included pathologic stage, grade, proliferation index, and the proportion of benign to malignant tumor (9).

Carcinosarcoma

Introduction. Carcinosarcoma is defined as "a malignant tumor composed of a mixture of both carcinomatous and sarcomatous elements" (1). Synonyms include true malignant mixed tumor and sarcomatoid carcinoma (see discussion of terminology in the section "Salivary Duct Carcinoma").

Clinical features. Carcinosarcoma is a very rare tumor, which accounts for only 0.2% of malignant tumors of major salivary glands (2) and to date, there have been over 70 published cases (2–22). Two-thirds have arisen in the parotid, approximately 19% in the submandibular glands and 14% in the palate (1) and a single case has been reported in the tongue (5). The mean age at presentation was 58 years

with a range of 14 to 90 years and there appears to be no significant sex predilection (2). Most cases appear to arise de novo but occasionally there is a history of a concurrent or recurrent pleomorphic adenoma (6). In these cases, the tumor should strictly be termed carcinosarcoma ex pleomorphic adenoma. Carcinosarcoma usually presents clinically as a mass, which may be painful. Nerve palsy, fixation, and ulceration are common, but regional lymph node involvement is infrequent (8).

Pathology. Carcinosarcoma is a biphasic tumor composed of a mixture of carcinomatous and sarcomatous elements, usually with a predominance of the sarcomatous component. The most common sarcomatous elements are chondrosarcoma, osteosarcoma (Fig. 141), and fibrosarcoma; moderate to poorly differentiated adenocarcinoma (NOS) (Fig. 142), or an undifferentiated carcinoma are the most common carcinomatous components. More

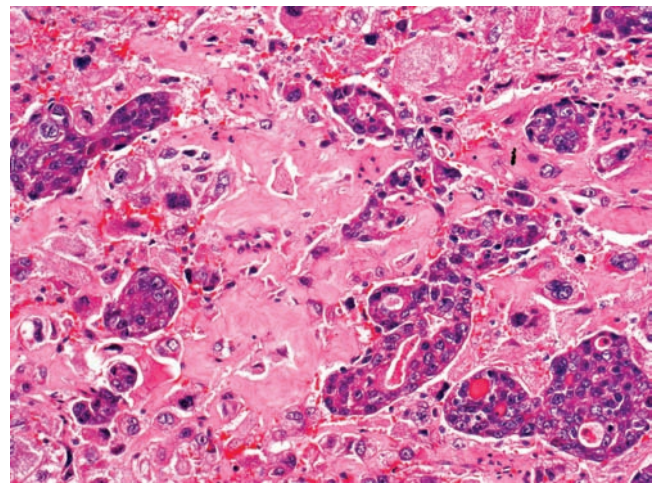


Figure 141 Carcinosarcoma showing mixture of adenocarcinomatous and osteosarcomatous differentiation.

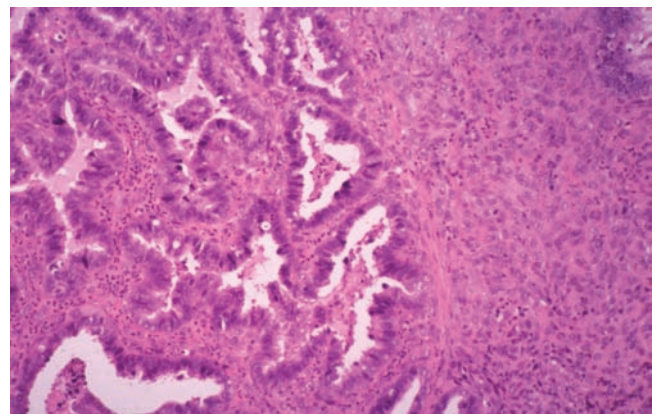


Figure 142 Carcinosarcoma showing poorly differentiated adenocarcinoma and sarcomatoid stroma.

defined carcinomatous elements such as salivary duct carcinoma (8) (see page 573), adenoid cystic carcinoma (19), and squamous cell carcinoma (17) can also be present. An unusual and unique case of a carcinosarcoma composed of a large cell neuroendocrine carcinoma and a rhabdomyosarcoma has been reported (10). Carcinosarcoma is characterized by local tissue infiltration and destruction (1).

Molecular-Genetic data. There have been few studies on the genetic profile of salivary carcinosarcomas. Loss of heterozygosity (LOH) at 17p13.1, 17q21.3, and 18q21.3 has been reported in a single tumor, indicating allelic loss in both components of a carcinosarcoma (11). P53 did not appear to be the target gene affected by the LOH at 17p13.1. However, in an immunohistochemical study, both components of a carcinosarcoma strongly expressed p53 (17). LOH at 17q21 and 9q21 has also recently been reported in several other carcinosarcomas, and the mutational profile was conserved between the carcinomatous and sarcomatous elements (18). These observations support the concept that the sarcomatous and carcinomatous elements of carcinosarcoma are derived from a common clonal precursor and do not represent a collision tumor. It has been suggested that the myoepithelial cell is the most likely common stem cell (11).

Treatment and prognosis. Treatment is usually wide surgical excision combined with adjuvant radiotherapy. There is a high mortality with almost 60% of patients dying from the disease with an average survival period of only 2.5 years (2). Two-thirds of patients develop local recurrence, and metastatic disease to lungs, bones, and central nervous system is seen in about half the patients (2,6–8,15).

Metastasizing Pleomorphic Adenoma

Introduction. Metastasizing pleomorphic adenoma has been defined as “a histologically benign pleomorphic adenoma that inexplicably manifests local or distant metastasis” (1). Synonyms include metastasizing benign mixed tumor and malignant mixed tumor.

Clinical features. The metastasizing pleomorphic adenoma is rare. In a recent review of the English literature, 42 cases of metastasizing pleomorphic adenoma were identified (2) and further cases have been reported (3,4). It is the least common of the three types of malignancy associated with pleomorphic adenoma (2,5). The average age at presentation is 33 years and there appears to be no significant sex predilection. Most cases arise in the parotid gland, with the remainder involving the submandibular gland and palate (6–11). There is usually a long history of a pleomorphic adenoma with multiple recurrences before the development of locoregional and/or distant metastases. The mean time from initial presentation to the development of metastatic disease was 16 years (2) with a range from 1.5 to 55 years.

Pathology. Both the primary tumor and the metastatic deposits consist of histologically typical benign pleomorphic adenoma (Fig. 143). There is no relationship between the histologic subtype type of pleomorphic adenoma and its propensity for malignant dissemination. Although mitotic figures and nuclear pleomorphism can be present, by definition, there is no evidence of frank malignancy although this assertion has been questioned (12). It has been postulated that the multiple recurrences and subsequent surgical interference result in the tumor gaining

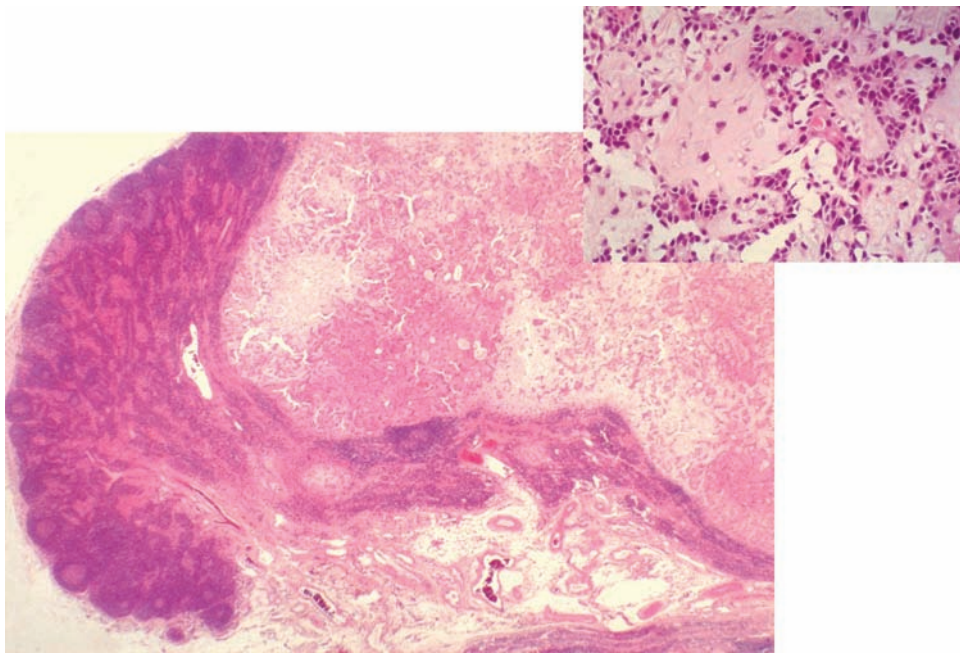


Figure 143 Metastasizing pleomorphic adenoma. Cytologically benign pleomorphic adenoma metastatic to supraclavicular lymph node.

lymphatic or venous access and allowing the cytologically benign tumor metastasize.

Immunohistochemistry. The immunohistochemical features are similar to those of conventional pleomorphic adenoma.

Molecular-genetic data. There have been limited genetic studies on these tumors. The majority of cases are found to have a normal diploid complement but in one study 2/11 cases showed aneuploid DNA (9). Karyotypic chromosomal analysis and fluorescent in situ hybridization in a single case have shown numerous translocations. These have included unbalanced rearrangements of chromosomes 1-13 and 9-21 and monosomy 22. These differ from the typical balanced 8q or 12q translocations associated with conventional pleomorphic adenoma (13). It has been suggested that genetic factors rather than coincidence or mechanical dislodgement may be involved in the metastatic progression in these tumors.

Treatment and prognosis. The main sites of metastasis are bone (45%), locoregional head and neck (43%), and lung (36%) (2). Distant spread is associated with a significantly adverse outcome with five-year disease-specific and disease-free survivals of only 58% and 50%, respectively. Other indicators of poor prognosis include the development of distant metastases within 10 years of the initial diagnosis of pleomorphic adenoma and the presence of metastases in multiple sites. Radical surgery is the treatment of choice as the evidence for the value of radiotherapy or chemotherapy is minimal.

Squamous Cell Carcinoma

Introduction. Squamous cell carcinoma has been defined as "a primary malignant epithelial tumor composed of epidermoid cells, which produce keratin and/or demonstrate intercellular bridges by light microscopy" (1). The diagnosis of a primary squamous cell carcinoma of salivary glands is often restricted to the major glands as there may be no reliable way of distinguishing tumors developing in minor glands from those of mucosal origin (1). In addition, it is essential to exclude metastases from the skin of the scalp, external ear, and face, or rarely, tumors arising in the upper aerodigestive tract. Similarly, direct extension from the overlying skin or external auditory meatus should be excluded (2).

Clinical features. Primary squamous cell carcinoma of the major salivary glands is uncommon and probably accounts for less than 1% of salivary gland tumors. There is a wide range of reported incidence, varying from 0.3% to 9.8% of all parotid malignancies and 2.1% to 11.4% of malignant submandibular gland tumors (3-8). The higher incidence rates for parotid tumors are probably due to the inclusion of cutaneous metastases (8-10). In addition, the possibility of direct extension from a squamous cell carcinoma of the floor of the mouth needs to be excluded in submandibular tumors. About 80% of cases involve the parotid gland, and 20% arise in the submandibular gland. Rare squamous cell carcinomas of Stensen's duct (11) and the accessory parotid duct epithelium (2) have been

reported. There is a male-female ratio of about 2:1. Most cases arise in the 50- to 70-year age range with a mean of 60 to 65 years (1); tumors in children are exceptional (12,13). Some tumors are associated with previous radiotherapy, often following a long latent period (5,7,14). About half of the patients present with a painless mass (5-7), and others give a history of a rapidly enlarging mass, which may be associated with pain, fixation, and facial nerve palsy. Many cases present with a high clinical staging (5-7).

Pathology. Grossly, most tumors form firm masses that are larger than 3 cm in diameter and show evidence of invasion. The cut surface is usually white or light gray, and there may be areas of necrosis. Histologically, the tumor is similar to other squamous cell carcinomas of the head and neck region (Figs. 144,145). Most are well or moderately differentiated, with less than 10% of poorly differentiated tumors (14). There may be ductal dysplasia and squamous metaplasia. There is usually extensive local invasion, and perineural involvement is common.

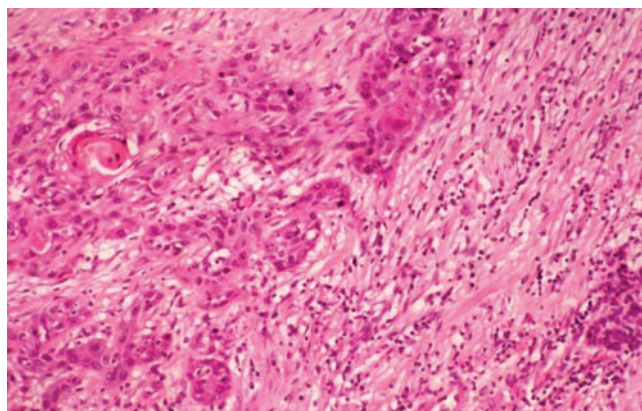


Figure 144 Moderately well-differentiated squamous cell carcinoma of the parotid gland.

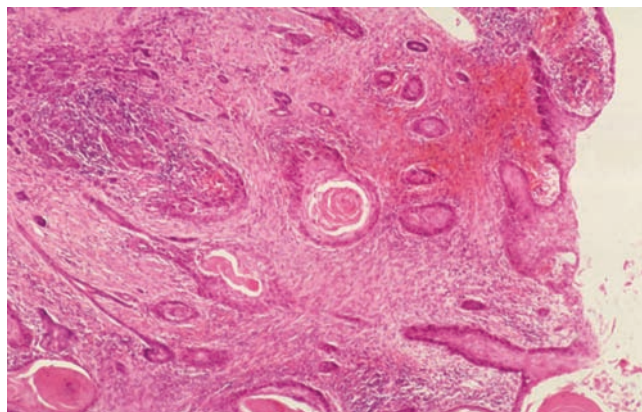


Figure 145 Well-differentiated squamous cell carcinoma arising from Stensen's duct.

Table 9 Differences in Clinicopathologic Characteristics of Three Types of “Undifferentiated Carcinomas”

	Small cell carcinoma	Large cell carcinoma	Lymphoepithelial carcinoma
Incidence	Rare (No ethnic predilection)	Rare (No ethnic predilection)	Rare (High in Inuit and Southern Chinese)
Association with EBV	No	No	Yes
Histopathology			
Cell size	Small	Large	Large
Nucleolus	Inconspicuous	Prominent	Prominent
Lymphoid stroma	No	No	Yes
Neuroendocrine differentiation	Yes	Sometimes	No
Prognosis	Poor	Poor	Fair

Abbreviation: EBV, Epstein–Barr virus.

Molecular-genetic data. There have been few cytogenetic studies of primary squamous cell carcinomas of salivary glands. However, deletions at 6q have been reported by several groups (15–17). This deletion has been noticed in other salivary gland tumors, but is uncommon in squamous cell carcinomas from elsewhere in the aerodigestive tract.

Differential diagnosis. The main differential diagnoses are metastatic squamous cell carcinoma and mucoepidermoid carcinoma. Occasionally, salivary duct carcinomas and oncocytic carcinomas may have an epidermoid appearance, but there are usually more typical areas elsewhere in the tumors. Mucoepidermoid carcinoma shows a wider range of cell types that include mucocytes, which can be demonstrated by appropriate stains. In addition, conspicuous keratinization is extremely uncommon in mucoepidermoid carcinomas. There can be striking pseudoeitheliomatous hyperplasia and, occasionally, necrotizing sialometaplasia in surgically treated or infarcted tumors. Careful examination and an accurate clinical history should prevent confusion. In addition, squamous cell carcinoma may be a component of carcinomas arising in both pleomorphic adenoma and Warthin’s tumor. Keratocystoma, a rare salivary gland neoplasm, should also be considered in the differential diagnosis (18). Keratocystoma is composed of multiple cysts lined by cytologically bland stratified squamous epithelium and filled with laminated keratin. There may be solid nests of squamous epithelium, but there is no evidence of invasion (see page 539).

Treatment and prognosis. Primary squamous cell carcinoma is usually a high-grade tumor. There is widespread invasion and frequent lymph node involvement at the time of presentation (5,7,10,19). About half the patients develop locoregional recurrence, and the five-year survival rates varied from 21% to 50% in two major series (5,7). Patients have usually been treated by surgery, with or without adjuvant radiotherapy. Because of the high rate of regional lymph node metastasis, elective neck dissection should be considered. The most important prognostic factor is clinical stage. Other reported adverse factors include patients over 60 years, ulceration, and fixation (7). In parotid gland tumors, facial nerve palsy and treatment modalities were also considered to be prognostic indicators (4,10).

“Undifferentiated Carcinomas”

Undifferentiated carcinomas of the salivary glands are uncommon high-grade malignant tumors that include malignant epithelial neoplasms too poorly differentiated by their light microscopic features to be placed in a specific category of carcinoma (1). They are generally subclassified into three groups: small- and large-cell types of undifferentiated carcinomas (2) and lymphoepithelial carcinoma. However, since epidemiologic, etiologic, and clinical features among these entities are different, each of them should be regarded as an independent tumor group (3–6) (Table 9).

Small Cell Carcinoma

Introduction. The small-cell type of undifferentiated carcinoma, usually simply called small cell carcinoma, of the salivary glands is rare. Small cell carcinomas are defined as “malignant epithelial tumors characterized by a proliferation of small anaplastic cells with scant cytoplasm, fine nuclear chromatin, and inconspicuous nucleoli” (4). On the basis of immunohistochemical and/or ultrastructural features, these tumors may be subclassified into two main types: neuroendocrine and nonneuroendocrine (ductal) types (1). However, most small cell carcinomas exhibit neuroendocrine differentiation (7,8). Neuroendocrine carcinomas may be further subdivided into cutaneous (Merkel cell) and pulmonary varieties on the basis of cytokeratin 20 immunoreactivity (8,9). Metastatic small cell carcinoma or cutaneous neuroendocrine carcinoma (Merkel cell carcinoma) should be ruled out before making a diagnosis of salivary gland small cell carcinoma.

Clinical features. Small cell carcinoma most frequently arises in the lung. An extrapulmonary origin is uncommon, and small cell carcinomas originating in the salivary glands are extremely rare, accounting for less than 1% of all salivary gland tumors and approximately 2% of salivary gland malignancies (3). Less than 80 cases of major salivary gland small cell carcinoma have been reported (2,8–23). Small cell carcinoma occurs slightly more commonly in males, with peak incidences in the fifth and seventh decades of life; however, these tumors have also been described in younger patients. Most involve the parotid gland, but a few cases in the submandibular gland and minor salivary glands have

also been reported. Patients typically present with a painless, rapidly growing mass of several months' duration. Cervical lymphadenopathy and facial nerve palsy are common findings. Paraneoplastic syndromes accompanied by the production of ectopic hormones are unusual in this tumor (22).

Pathology. Macroscopically, small cell carcinoma is a firm, poorly circumscribed tumor that often infiltrates the surrounding salivary gland parenchyma and adjacent soft tissues. The tumor is usually gray to white and commonly accompanied by necrosis and hemorrhage.

Histopathologically, all small cell carcinomas invade the surrounding normal salivary gland or adjacent adipose or muscular tissue. Small cell carcinoma is characterized by sheets, cords, or irregular nests of anaplastic, small-sized tumor cells and a variable amount of fibrous stroma. Tumor cell nests may exhibit a peripheral palisading pattern. An organoid pattern and rosette-like structures are occasionally seen. Tumor cells are usually roughly two times larger than mature small lymphocytes and contain round to fusiform hyperchromatic nuclei with scanty cytoplasm (Fig. 146A). These cytologic features closely resemble those of "oat cell carcinoma" of the lung. Some tumor cells are slightly larger and exhibit polygonal nuclei with more cytoplasm (although the tumor cells are still $<30\ \mu\text{m}$ in diameter) (Fig. 146B). They are similar to the intermediate cell variant of pulmonary small cell carcinoma or typical Merkel cell carcinoma. Regardless of cellular size, the nuclear chromatin is finely granular, and nucleoli are absent or inconspicuous. Cell borders are ill defined, and nuclear molding is common. Numerous mitotic figures are usually present. Crush artifacts are observed in most of the tumors. The tumor may have small foci of ductal differentiation or squamous differentiation. Extensive necrosis and vascular and perineural invasion are common.

Immunohistochemistry. In most small cell carcinomas, the tumor cells express neuroendocrine markers. The tumors usually stain positively for, in descending frequency, neuron-specific enolase, chromogranin A (Fig. 147A), synaptophysin, neurofilament, and CD56. However, immunoreactivity for neuron-specific enolase alone is insufficient evidence to confirm the neuroendocrine differentiation of the tumor. Most small cell carcinomas are positive for pancytokeratins, which sometimes have a characteristic paranuclear dot-like pattern of reactivity. About three-fourths of the tumors are immunoreactive for cytokeratin 20, frequently with a characteristic dot-like pattern (Fig. 147B) (8). They stain positively for cytokeratin 20 in the Merkel cell variety and negatively in the pulmonary variety. Positive neurofilament immunoreactivity, with a dot-like pattern, is seen in some cytokeratin 20-positive tumors. The majority of the tumors are also positive for epithelial membrane antigen. A few tumors express thyroid transcription factor 1 (8,24). Small cell carcinomas are negative for S-100 protein, HMB-45, and myoepithelial and lymphoid markers.

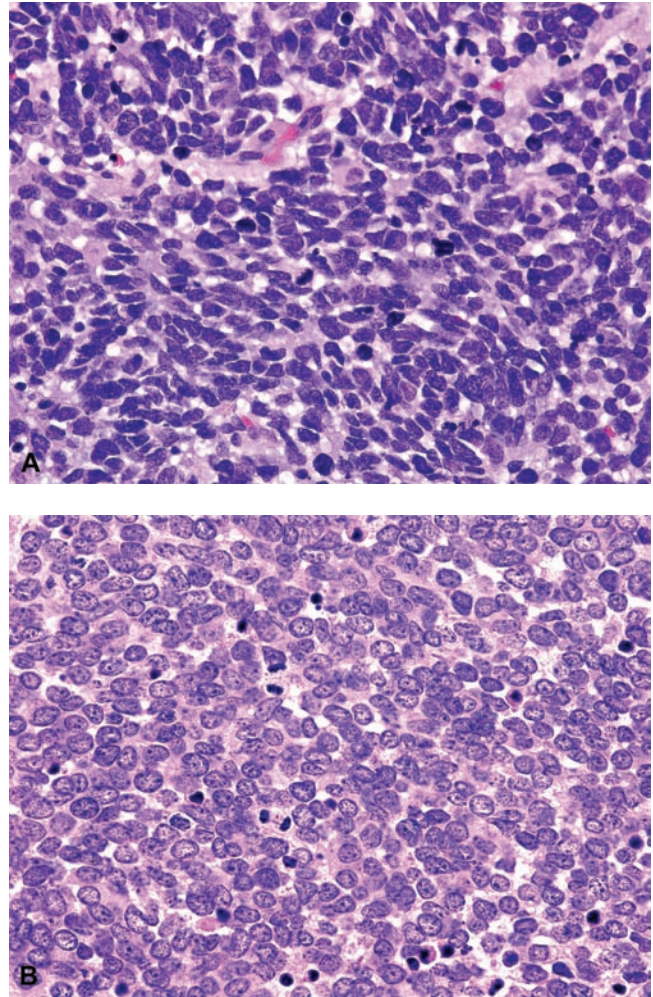


Figure 146 Small cell carcinoma. High-power view showing the tumor cells with scant cytoplasm and inconspicuous nucleoli. Mitotic figures are readily identified. (A) The tumor cells have elongated nuclei with granular, dense chromatin. These cytologic features closely resemble those of "oat cell carcinoma" of the lung. (B) The tumor cell nuclei are round to oval, with pale, dispersed chromatin and a well-defined nuclear membrane. They are similar to typical Merkel cell carcinoma of the skin.

Electron microscopy. Membrane-bound neuroendocrine granules are seen in about one-third of small cell carcinomas (7). The tumor cells contain sparse cytoplasmic organelles, and either poorly or well-formed desmosomes interconnect the cells. Multidirectional differentiation with the presence of myofilament-like microfilaments and tonofilaments has been reported (15,19).

Differential diagnosis. Before making a diagnosis of salivary gland small cell carcinoma, other types of small "blue cell" tumors should be excluded. These include the solid type of adenoid cystic carcinoma, malignant lymphoma, malignant melanoma, and metastatic pulmonary small cell carcinoma or Merkel cell carcinoma.

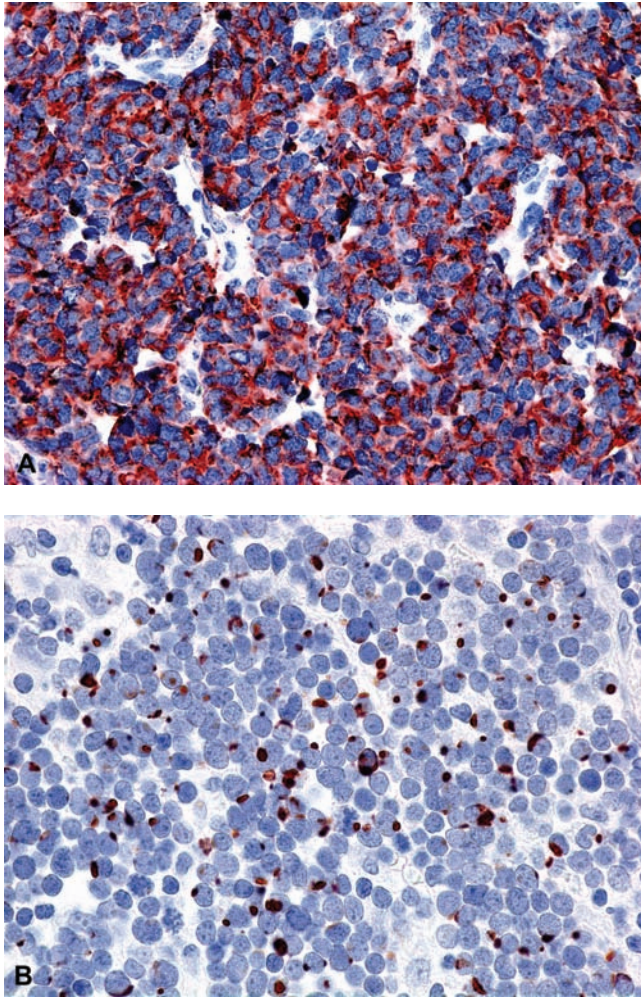


Figure 147 Small cell carcinoma. (A) Tumor cells are diffusely immunopositive for chromogranin A. (B) Paranuclear dot-like pattern of immunoreactivity for cytokeratin 20.

Distinction of solid adenoid cystic carcinoma from small cell carcinoma may be difficult. The solid type of adenoid cystic carcinoma has a focal cribriform architecture and lacks neuroendocrine differentiation and paranuclear dot-like cytokeratin positivity of small cell carcinoma. The presence of myoepithelial differentiation in this neoplasm also distinguishes it from small cell carcinoma. Positive cytokeratin staining and negative CD45 (leukocyte common antigen) expression exclude malignant lymphoma. Malignant melanoma can also show a small-cell morphology, but positive immunoreactivity for S-100 protein, HMB-45, Melan-A, and vimentin, and a lack of cytokeratin staining do not favor a diagnosis of small cell carcinoma.

Metastasis from small cell carcinoma of extra-salivary origin or Merkel cell carcinoma must also be excluded. A negative medical history of a previous or coexisting malignancy assists in resolving this diagnostic dilemma. In addition, a dot-like pattern of

positive immunoreactivity for cytokeratin 20 and neurofilament strongly favors salivary small cell carcinoma or Merkel cell carcinoma, features that are not detected in pulmonary small cell carcinoma, which is the most likely metastatic neoplasm (9).

Treatment and Prognosis. Small cell carcinoma of major salivary glands is a highly aggressive tumor, although the prognosis may be better than that for small cell carcinoma of bronchogenic or laryngeal origin. The two- and five-year survival rates for patients with salivary gland small cell carcinomas are 38% to 70% and 13% to 46% (8,13,18), respectively, compared with 16% and 5% for patients with similar tumors of the larynx (25). Distant metastases develop in more than 50% of patients after the initial diagnosis. Even though the incidence of cervical lymph node involvement is high, it may be exceeded by hematogenous metastasis. Overall survival is significantly reduced in patients with a primary tumor larger than 3 cm in diameter, a negative immunostain reaction for cytokeratin 20, and decreased immunoreactivity for neuroendocrine markers (8,17). Therefore, the immunohistochemical determination of the cytokeratin 20 expression of salivary gland small cell carcinomas is recommended, since the result could affect the prognosis. The treatment of choice is wide local excision with cervical lymph node dissection. Adjuvant chemotherapy and radiation therapy may be warranted.

Large Cell Carcinoma

Introduction. Large cell carcinomas are defined as "rare, high-grade malignant salivary gland epithelial tumors composed of large-sized pleomorphic cells with abundant cytoplasm" (1). This tumor lacks histologic features of other specific types of salivary gland carcinomas and was formerly called large cell undifferentiated carcinoma, a subtype of undifferentiated carcinomas (2–7). Salivary gland neuroendocrine carcinomas other than the small-cell type have received little attention until recently and were not recognized as a specific entity in the 2nd edition of WHO classification (7). Rarely, large cell carcinomas exhibit neuroendocrine differentiation, and these are now referred to as "large cell neuroendocrine carcinomas" (3,8–10). The absence of the components of any other specific tumor type should be confirmed by careful examination before making the diagnosis of salivary gland large cell carcinoma.

Clinical features. Large cell carcinomas account for less than 1% of all epithelial salivary gland neoplasms (1). In one report, 2 out of 13 cases of large cell carcinoma had neuroendocrine differentiation. To date, only five cases of large cell neuroendocrine carcinoma of the salivary glands have been reported (3,8–10). In the majority of cases, the patients are older than 60 years when the initial diagnosis is established. Men and women are affected equally. Unlike lymphoepithelial carcinoma, no ethnic predilection, familial occurrence, or association with EBV has been documented. The majority of large cell carcinomas arise in the major salivary glands, especially the

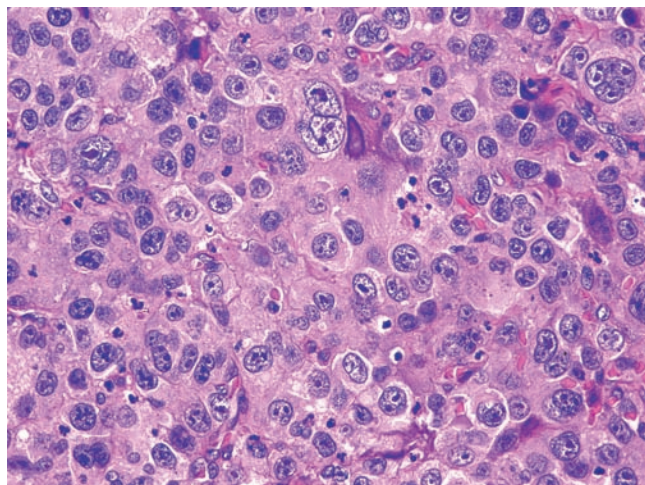


Figure 148 Large cell carcinoma. Sheet-like growth pattern of large pleomorphic cells with abundant eosinophilic cytoplasm and prominent nucleoli.

parotid. A few tumors of minor salivary gland origin have also been reported. Many patients present with a rapidly growing firm mass that is often fixed to adjacent tissue. Facial nerve paralysis and cervical lymph node enlargement are common findings.

Pathology. Large cell carcinoma is usually a poorly circumscribed, solid tumor with a grayish white or tan cut surface. The tumor is often over 3 cm in diameter, and necrosis and hemorrhage are frequent. Invasion into the adipose and muscular tissue adjacent to the salivary gland is common.

Microscopically, the tumor growth pattern consists of sheets (Fig. 148) and trabeculae, with a conspicuous tendency for necrosis. Organoid, rosette-like, and peripheral palisading patterns characterize large cell neuroendocrine carcinomas (Fig. 149). By definition, large cell carcinoma is too poorly differentiated to allow more specific classification, but very rare foci of ductal or squamous differentiation may be identified, and the presence of these features do not preclude the diagnosis of large cell carcinoma.

The tumor is composed of large pleomorphic cells ($>30\ \mu\text{m}$ in diameter) with an abundance of eosinophilic or occasionally clear cytoplasm. The tumor cell nuclei have a polygonal or fusiform shape, prominent nucleoli, and coarse chromatin with vesicular distribution. While cell borders are usually well defined, bizarre or osteoclast-like giant cells may be present (11). Cytoplasmic glycogen can be shown by PAS staining, but there are no mucicarmine-positive goblet-type mucous cells. Mitotic figures are readily identified and are frequently numerous. The amount of fibrous stroma varies, and unlike lymphoepithelial carcinoma, lymphoid cell infiltration is usually focal and patchy. Perineural and vascular invasion is prominent.

Components of other categories of salivary gland neoplasms must not be present because an

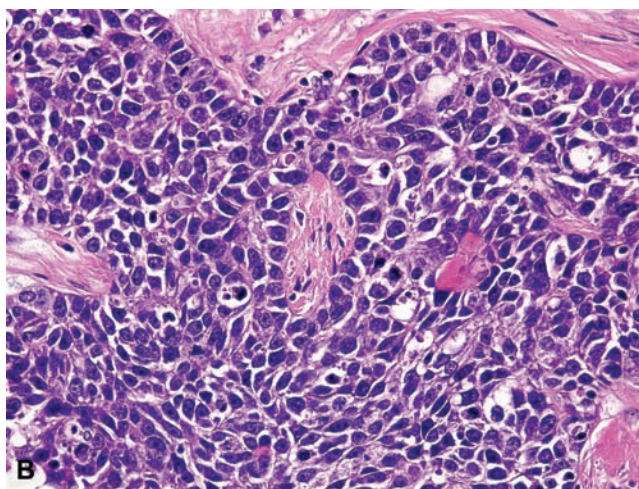
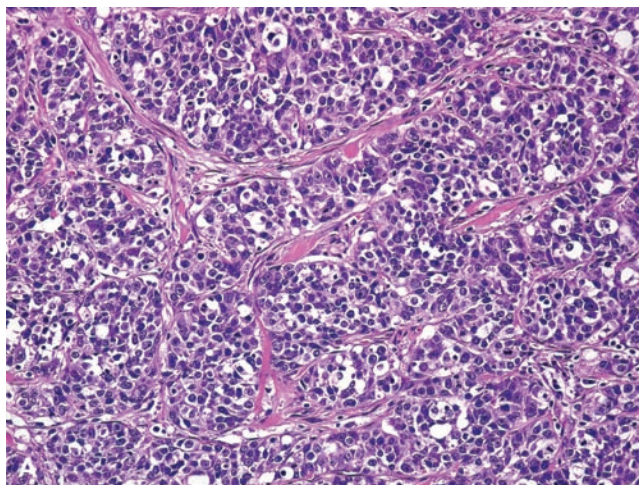


Figure 149 Large cell neuroendocrine carcinoma. (A) Organoid growth pattern. (B) Solid growth with peripheral palisading and several rosette-like structures. The tumor cells have large and polygonal nuclei with vesicular chromatin and prominent nucleoli.

undifferentiated carcinoma with large cells can occur in association with various benign and malignant neoplasms, including pleomorphic adenoma (12), acinic cell carcinoma (13), mucoepidermoid carcinoma (14), adenoid cystic carcinoma (15), epithelial-myoepithelial carcinoma (16), polymorphous low-grade adenocarcinoma (17), and salivary duct carcinoma.

Immunohistochemistry. Large cell carcinoma cells are usually positive for cytokeratins and epithelial membrane antigen but never positive for lymphoid markers, HMB45, or smooth muscle actin. In large cell neuroendocrine carcinomas, tumor cells should be positive for at least one neuroendocrine marker, including chromogranin A, synaptophysin, or CD56 in addition to neuron-specific enolase. No immunoreactivity for cytokeratin 20 is found. The Ki-67 labeling index is high and often greater than 50%. In two reported cases of large cell neuroendocrine carcinoma, the tumor cells showed diffuse

immunoexpression of bcl-2 protein, epidermal growth factor receptor, and cyclin D1, and reduced immunoexpression of p21/waf1 and p27/kip1 (9). Diffuse p53 nuclear immunoexpression has been found in four of five cases (9,18,19). Expression of c-erbB-2 has been identified in the majority of tumors.

Electron microscopy. Tumor cells occasionally have a squamous or glandular differentiation not apparent on conventional light microscopic examination (20). Neuroendocrine differentiation with the presence of neurosecretory granules has rarely been described (3,8,9). Prominent desmosome-like junctions connect the tumor cells.

Differential diagnosis. Metastatic undifferentiated carcinoma, particularly from the nasopharynx to the parotid gland, must first be excluded. Clinical information is necessary in differentiating between a primary and a metastatic origin. Since an undifferentiated carcinoma with large cells can be found in carcinoma ex pleomorphic adenoma and various types of dedifferentiated carcinomas, the absence of a component of other specific tumor types should be confirmed by a careful search before arriving at the diagnosis of salivary gland large cell carcinoma. The epithelioid-cell type of myoepithelial carcinoma can be distinguished from large cell carcinoma by immunostaining for smooth muscle actin and calponin. Metastatic malignant melanoma must also be differentiated from large cell carcinoma (21). Immunohistochemical staining for cytokeratin, S-100 protein, HMB-45, and Melan-A distinguishes these tumors. Anaplastic large cell lymphoma involving parotid gland lymph nodes may be necessary for a differential diagnosis with large cell carcinoma. Immunohistochemical staining for cytokeratin and lymphoid markers including CD30 can resolve this diagnostic problem. Negative immunoreactivity for cytokeratin 20 in large cell neuroendocrine carcinoma helps to exclude the possibility of Merkel cell carcinoma.

Treatment and Prognosis. Large cell carcinoma is an aggressive tumor with a propensity for local recurrence, cervical lymph node metastasis, and distant spread. One series has shown that the two-year survival rate is only 36% (22). Large cell neuroendocrine carcinoma is also a high-grade tumor. Tumor size is a prognostic indicator; all patients with tumors larger than 4 cm died from their disease after developing distant metastases (3). An age of more than 50 years is also associated with a significantly poorer prognosis for patients with large cell carcinoma (3). One study has shown that cell size (small- vs. large-cell type of undifferentiated carcinoma) has no influence on prognosis (3). Radical surgical excision with neck dissection and postoperative radiotherapy is the treatment of choice.

Lymphoepithelial Carcinoma

Introduction. Lymphoepithelial carcinoma (1–7) is also known as undifferentiated carcinoma with lymphoid stroma (8–10), lymphoepithelioma-like carcinoma (11,12), and malignant lymphoepithelial lesion (13–19). It has been defined as “an undifferentiated

carcinoma accompanied by a prominent nonneoplastic lymphoplasmacytic infiltrate” (7). Lymphoepithelial carcinomas of the salivary glands show histologic features that are almost identical with those of nasopharyngeal origin.

Most lymphoepithelial carcinomas develop de novo (10), but an association with a preexisting lymphoepithelial sialadenitis (LESA) or “benign lymphoepithelial lesion” may rarely be encountered (20). However, the issue concerning the pathogenetic correlation between these lesions needs to be resolved, and whether malignant transformation of LESA actually occurs has not been established (10).

Clinical features. Lymphoepithelial carcinomas are rare, usually accounting for less than 1% of all salivary gland tumors, although an exceptionally high incidence has been reported among Mongolians, particularly Inuit (15,17,18,21–24) and Southern Chinese populations (1,2,6,12,16,19,25,26). Approximately 75% of reported cases have occurred in these races. Familial clustering of salivary gland lymphoepithelial carcinoma has been reported (27,28). Although Japanese are also ethnic Mongolians, lymphoepithelial carcinoma is quite rare in Japan (10).

The tumor occurs in patients of a wide age range, from the first to the ninth decades (median, 40 years), with a slightly higher incidence in females. Lymphoepithelial carcinomas most frequently involve the parotid gland (over 90% of the cases), followed by the submandibular gland. Rarely, the intraoral minor salivary glands are affected (5,11). Patients present with an enlarging, firm mass, which may have a long-standing history with a recent rapid increase in size. Facial nerve palsy is seen in up to 20% of the cases, and cervical lymph node enlargement is present in about 40% of the patients (7). There is no clinical association with Sjögren syndrome or malignant lymphoma.

Lymphoepithelial carcinoma in the salivary gland is consistently associated with EBV in Mongolian patients but usually not in Caucasian patients (1–6,10,12,18,19,23,25,26,29,30). More than 50% of these patients (all Mongolian) have elevated titers of serum immunoglobulin A against EBV capsid antigen (7). Therefore, ethnic, geographic, and genetic factors may influence EBV infection, which leads to the development of lymphoepithelial carcinoma of the salivary glands. The presence of the virus in a clonal episomal form suggests that EBV may have an etiologic role in the development of lymphoepithelial carcinoma (2).

Pathology. Macroscopically, the tumors are a solid and firm mass ranging in size from 1 to 10 cm. On cut section, they may be circumscribed and even partially encapsulated, but typically extensive infiltration of salivary gland and adjacent soft tissues is evident.

Histologically, lymphoepithelial carcinoma is characterized by cluster formation of large anaplastic carcinoma cells enclosed within a prominent sheet of lymphoid cells (Fig. 150A, B). Although the lesions are sometimes circumscribed, carcinoma cells often infiltrate into the surrounding salivary gland tissues accompanied by a lymphoid stroma. The carcinoma

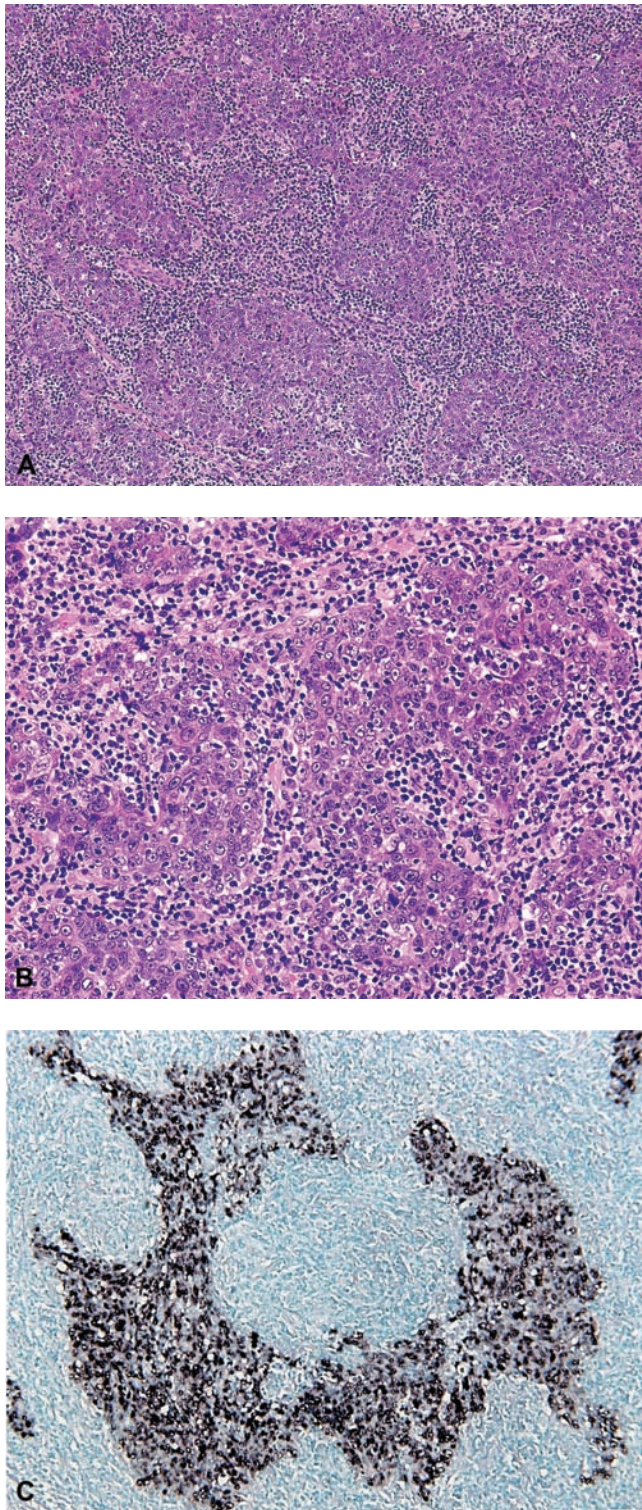


Figure 150 Lymphoepithelial carcinoma. (A) Solid, trabecular, or irregular arrangements of carcinoma cells enclosed within a lymphoid stroma. (B) The carcinoma cells are large and create a syncytial appearance. Nuclear chromatin is vesicular and there are prominent nucleoli. (C) In situ hybridization for EBV-encoded small RNA (EBER). Almost all of the carcinoma cells express strong nuclear EBER hybridization signals. Note complete absence of signal in the surrounding lymphoid stroma.

cells show solid, trabecular or irregular arrangements. Their cytoplasmic borders are indistinct and frequently create a syncytial appearance. Reactive histiocytes have been reported to impart a “starry sky” pattern within tumor islands (16).

Usually, the carcinoma cells are large and polygonal or sometimes spindled (18). Nuclear chromatin is vesicular or clumped, and there are prominent eosinophilic nucleoli. The cytoplasm of the tumor cells may be relatively abundant and slightly amphophilic. A number of mitotic figures are usually evident. Although ductal structures are absent and no intra-cytoplasmic mucin is identified in the tumor cells, focal squamous differentiation with keratinization may be present.

Lymphoid follicles, each with a germinal center, are occasionally observed in the lymphoid tissue. A fibrous stroma is sometimes seen. Rarely, carcinoma cells form clearly defined islands, which show peripheral palisading with PAS-positive hyaline material (10,24). Perineural invasion is a common finding. Generally, the residual salivary gland shows various degrees of lymphocytic infiltration. Benign epimyoepithelial islands may be identified in the surrounding salivary gland tissue in occasional cases (20).

Electron microscopic features indicate that lymphoepithelial carcinoma is a poorly differentiated squamous cell carcinoma with variable amounts of tonofilament bundles and well-formed desmosomes (10,31).

Immunohistochemistry. Carcinoma cells are positive for pan-cytokeratin and epithelial membrane antigen but are negative for lymphoid markers. They usually show diffuse expression of p53 and high Ki-67 labeling index with over 40% (10). The lymphoid cells are polyclonal in nature with a mixture of B cells and T cells. Expression of EBV latent membrane protein 1 varies (2,32). In Mongolians, EBV can almost always be detected in the nuclei of almost all carcinoma cells using in situ hybridization technique (Fig. 150C) (1–6,10,12,18,19,25,26,29,30). No hybridization signals are identified in the lymphoid stroma or the surrounding non-tumorous salivary gland tissue. BamHI H left frame 1 (BHLF1) mRNA signals, on the other hand, are not detectable in any tumors (10).

Differential diagnosis. The differential diagnosis should include metastatic lymphoepithelial carcinoma, LESA, large cell carcinoma, malignant lymphoma, and lymphadenoma.

Since lymphoepithelial carcinoma of the salivary glands is histologically indistinguishable from lymphoepithelial carcinoma of nasopharyngeal origin, which is much more commonly seen, nasopharyngeal lymphoepithelial carcinoma should be excluded by careful clinical examination along with multiple random biopsies at the site. However, nasopharyngeal lymphoepithelial carcinoma metastatic to the salivary glands is an extremely rare event.

LESA has a histologic architectural structure, with epithelial and lymphoid components similar to those of lymphoepithelial carcinoma. Bland cytologic features, low mitotic activity, the presence of hyaline material deposition, and the absence of invasive

growth pattern favor a diagnosis of LESA, rather than lymphoepithelial carcinoma. Especially when only small tissue fragments are available for histologic examination, the presence of EBV demonstrated by EBER in situ hybridization, the diffuse expression of p53, and a high cell proliferative activity assessed by Ki-67 immunostaining may be useful for distinguishing lymphoepithelial carcinoma from LESA (10).

The distinction of lymphoepithelial carcinoma from large cell carcinoma is important because the prognosis of these two entities is quite different (6). Large cell carcinomas are not associated with any significant degree of lymphoid infiltrate and do not show intermingling pattern of the carcinoma cells and lymphoid cells as seen in lymphoepithelial carcinoma.

Malignant lymphoma, especially of diffuse large-cell type, can be distinguished from lymphoepithelial carcinoma by immunostaining for pan-cytokeratins and lymphoid markers, such as CD45 (leukocyte common antigen), CD20, CD79a, and CD30. Lymphadenoma, a recently defined rare tumor entity, shows ductal formation without cytologic atypia and is negative for EBER in situ hybridization (33).

Treatment and Prognosis. The five-year survival rate of patients with lymphoepithelial carcinoma of the salivary glands is between 75% and 86% (7), which is much better than the outcome of patients with large cell carcinoma (6). Lymph node metastases are a common finding, and distant metastasis can be found in 20% of the patients (7). Prognostic factors include tumor stage and histologic features. One study on Alaskan natives subclassified the tumor into low- and high-grade types on the basis of histologic features and prognosis (24). Radical surgical excision with postoperative radiation therapy is the best choice of treatment. Most lymphoepithelial carcinomas are radiosensitive.

Sialoblastoma

Introduction. Sialoblastoma has been defined as “a rare, potentially aggressive, parotid or submandibular gland tumor that is usually present at birth and recapitulates the primitive salivary anlage” (1). Synonyms include congenital basal cell adenoma, basaloid adenocarcinoma, congenital hybrid basal cell adenoma–adenoid cystic carcinoma, and embryoma (2–5).

Clinical features. Sialoblastomas are very rare, with about 40 cases in the literature (2–24). Most have been reported as single cases, but there is a short series of seven cases from the files of the AFIP (23). Most tumors are evident at birth or within the first few months of life, with occasional cases in the second and third years of life (4,7,12,21). Cases have been detected in utero (16). There is no significant sex predilection. Three quarters of tumors have arisen in the parotid gland, with the remainder in the submandibular gland. A similar tumor has been reported in the eyelid (25). Sialoblastoma usually presents as a painless, firm swelling, but some have shown ulceration and facial nerve involvement. Cases of coexistent congenital nevi (7,9) and hepatoblastoma have been reported

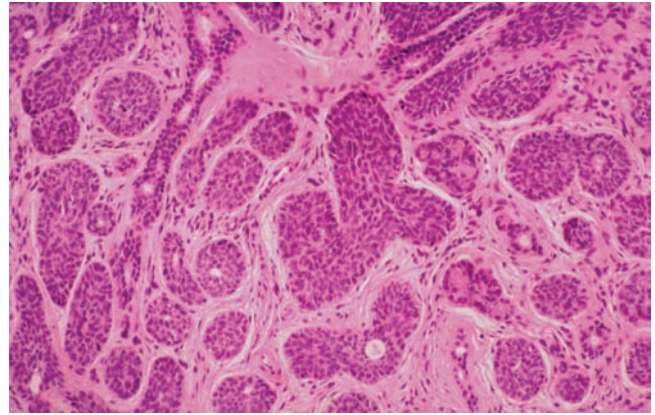


Figure 151 Sialoblastoma (embryoma). Well-differentiated tumor consisting of solid basaloid, duct-like structures, and clusters of acinar type cells in fibrous stroma.

(19). A single tumor was associated with a high level of serum α -fetoprotein and premature centromere division (16).

Pathology. Macroscopically, the tumors range from 1.5 to 15 cm and appear to be partially encapsulated, firm swellings that may show local infiltration (26). They are multilobulated, and the cut surface is usually tan or yellow and solid. Occasionally, there are areas of hemorrhage or necrosis. Microscopically, the tumor consists of primitive, basaloid epithelial cells (Fig. 151). The nuclei are round or oval and vesicular with occasional nucleoli. The eosinophilic cytoplasm varies from scanty to abundant and usually has indistinct borders. There is variable pleomorphism, and some cells have hyperchromatic nuclei, a high nuclear-cytoplasmic ratio, and numerous, typically normal mitoses (Fig. 152). Apoptosis and necrosis may be present. The cells are usually arranged in solid,

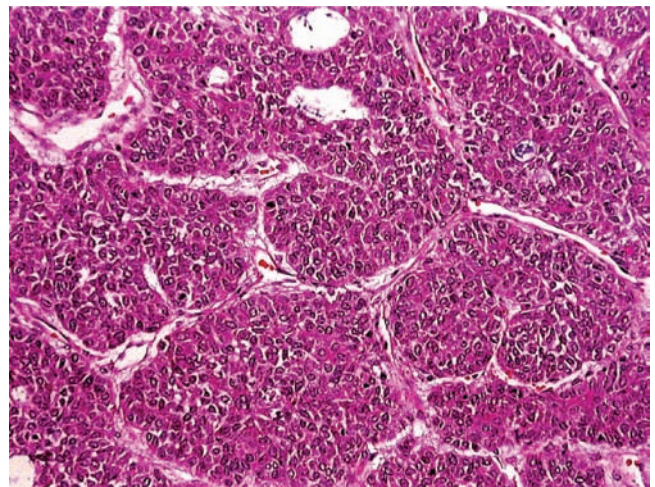


Figure 152 Sialoblastoma (embryoma). Poorly differentiated tumor consisting of solid nests of basaloid cells.

hypercellular nests, and the outer layer may show nuclear palisading. There may be small, duct-like structures lined by cuboidal cells, occasionally associated with solid, acinar-like nests resembling the anlage of the developing salivary gland. Myoepithelial cells have been associated with these structures, and focal areas of sebaceous or squamous differentiation may be present (17,18). Cribriform areas may be seen focally, and occasionally, calcospherites are present. The stroma is variable and can consist of thin, fibrous septa, sparsely cellular myxoid tissue or more primitive, abundant, and cellular fibroblastic areas.

Immunohistochemistry. Sialoblastoma is positive for a variety of keratin markers, including pan-cytokeratin cocktail, epithelial membrane antigen, cytokeratins 5/6, 7, and 14, but negative for cytokeratin 20 (3,11,18,23). The abluminal cells stain with a variety of myoepithelial markers including smooth muscle actin, calponin, S-100 protein, cytokeratin 14, p63, and pan-cytokeratin (18). α -fetoprotein reactivity has been reported (16,23), but tumors are negative for glial fibrillary acidic protein (11,23). There is a wide variation in Ki-67 expression (3–80%) (23).

Differential diagnosis. Sialoblastoma needs to be distinguished from other basaloid neoplasms, including basal cell adenoma, basal cell adenocarcinoma, and adenoid cystic carcinoma. The degree of cytologic atypia, primitive cellular features, mitotic frequency, and local infiltrative growth pattern are not seen in basal cell adenoma, and this tumor is exceptional in children. Basal cell adenocarcinoma and adenoid cystic carcinoma are also not seen in the perinatal period.

Treatment and Prognosis. Sialoblastoma is an aggressive and potentially low-grade malignant neoplasm. About 20% of cases recur, and occasionally, the tumor metastasizes to regional lymph nodes or distant sites (12,23,27). Their relative rarity makes it difficult to make accurate prognostic statements. However, on the basis of an admittedly small series, it has been suggested that sialoblastomas can be divided into favorable and unfavorable subtypes on the basis of their histology (23). Favorable tumors are partially capsulated, cytologically relatively bland, and have abundant stroma. Unfavorable tumors consist of anaplastic, basaloid cells, have minimal stroma, and may show evidence of vascular or perineural invasion. In addition, they may express α -fetoprotein reactivity and have a high Ki-67 proliferative index. Complete surgical excision appears to be the treatment of choice. Although the successful treatment of metastatic disease with adriamycin has been reported (20), the overall role of radiotherapy and chemotherapy is difficult to assess (17,23,27).

J. Hybrid Tumors

Introduction

Salivary gland tumors are known to have diverse histologic features, sometimes exhibiting combined histologic patterns observed in different tumor entities. In 1996, Seifert and Donath defined a salivary gland tumor entity characterized by containing two or

more histologically distinct types of tumor within the same topographical area and proposed the term "hybrid tumor" (1). Examples of both benign and malignant hybrid tumors have been reported, most being the latter and referred to as hybrid carcinomas.

Some controversial issues regarding the criteria for hybrid carcinomas have been raised. Since in the salivary glands, shared foci of similar phenotypic differentiation may be seen among the different histologic tumor types, Gnepp et al. proposed that in hybrid carcinomas, each element needs to differentiate toward distinctly different salivary gland elements: for example, excretory duct versus acini or excretory duct versus intercalated duct (2). Grenko et al. described three adenoid cystic carcinomas and two epithelial-myoepithelial carcinomas that focally shared both histologic features (3). They suggested that these two entities shared common differentiation pathways and did not categorize these examples as hybrid carcinomas. On the other hand, Seifert and Donath, and Croitoru et al. did not take account of the cellular phenotypes constituting hybrid tumors (1,4). Chetty et al. suggested that completely divergent differentiation may lead to the appearance of two distinct tumor entities (hybrid tumors), whereas incomplete divergence may lead to tumors harboring overlapping histologic features (5). It has been postulated that the two tumor components have an identical origin because of the consistent presence of a transitional zone between the two. We recommend that in hybrid carcinomas, each carcinoma component should occupy at least 10% of the tumor mass and should be separated from the other component (6).

Clinical Features

Hybrid carcinomas are very rare and, to the best of our knowledge, only 26 such cases have been described (1,3–13). The prevalence is up to 0.4% of all salivary gland tumors. In hybrid carcinomas, there is no gender predilection and an age range from 28 to 81 years (mean 59 years). In terms of tumor location, most hybrid carcinomas (17 cases) arise in the parotid gland with additional cases from the palate (5 cases), submandibular gland (2 cases), and lacrimal gland (1 case).

Pathology

Tumor size of hybrid carcinomas ranges from 2 to 10 cm (mean 4 cm). Microscopically, hybrid carcinoma shows a single tumor mass consisting of two distinct histologic types with invasion into the surrounding salivary gland tissue (Fig. 153). Various carcinoma combinations have been described in hybrid carcinomas (1,3–13); salivary duct carcinoma, epithelial-myoepithelial carcinoma, and adenoid cystic carcinoma are frequently involved. Others include mucoepidermoid carcinoma, acinic cell carcinoma, squamous cell carcinoma, basal cell adenocarcinoma, myoepithelial carcinoma, and polymorphous low-grade adenocarcinoma. Rare hybrid adenomas show combinations of basal cell adenoma with canalicular adenoma, Warthin's tumor with sebaceous adenoma, and Warthin's tumor with oncocytoma (1).

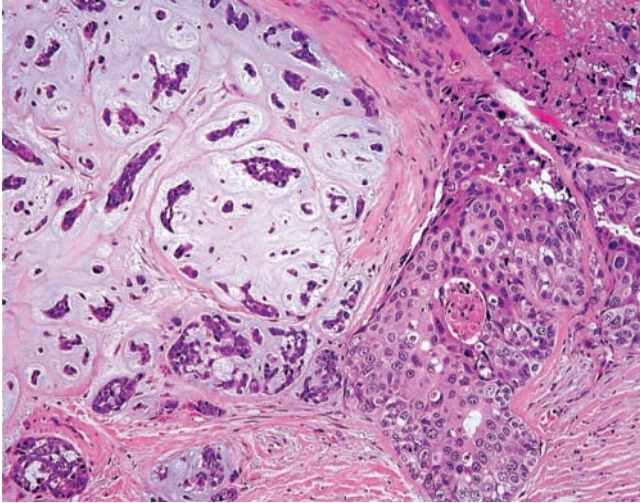


Figure 153 Hybrid carcinoma. Tumor consists of two distinct histologic types: salivary duct carcinoma composed of solid tumor nests with comedonecrosis (*right*) and myoepithelial carcinoma with myxoid stroma (*left*).

The proportion of each carcinoma component in a tumor mass varies from case to case, but, as noted above, the minor component should occupy at least 10% of the area. Although two distinct carcinoma components are recognized, a transitional zone between them is always present.

Immunohistochemistry

Immunohistochemically, Ki-67 labeling index commonly differs between the two carcinoma elements (6,8). It has been reported that diffusely positive p53 immunoreactivity was observed only in the histologically more aggressive component in each pair (6,8). Furthermore, these p53-positive cases demonstrated frequent loss of heterozygosity at p53 microsatellite loci and p53 gene point mutations, which were detected only in the p53-immunoreactive carcinoma component (6). Therefore, there is a possibility that such molecular-genetic events take an integral part for inducing the transformation from histologically lower to higher-grade tumor during the hybrid carcinoma oncogenesis.

Differential Diagnosis

The concept of hybrid carcinoma is subject to some confusion, and careful diagnosis is required. Several salivary gland tumor entities that exhibit two or more different morphologies should be ruled out before a diagnosis of hybrid carcinoma is made (1,14). These entities include collision tumors, synchronous and multiple tumors (14,15), carcinomas with metaplastic change, dedifferentiated carcinomas, and carcinomas arising from pleomorphic adenomas.

The presence of a transitional zone between the two carcinomatous components, suggesting their identical origin, differentiates hybrid carcinomas

from collision tumors, which are a meeting of two carcinomas arising from independent topographical sites, and from synchronous and multiple tumors. It has been reported that some salivary gland carcinomas may exhibit focal squamous, oncocytic, or sebaceous metaplasia (16–18). Obviously, such carcinomas with metaplastic changes should not be considered as containing two different carcinoma types. Some salivary gland carcinomas such as acinic cell carcinoma (19), adenoid cystic carcinoma (20–22), epithelial-myoepithelial carcinoma (23), and polymorphous low-grade adenocarcinoma (24,25) may rarely contain a dedifferentiated carcinoma component with aggressive growth. In contrast to the dedifferentiated element, which may be either undifferentiated carcinoma or poorly differentiated adenocarcinoma, hybrid carcinomas are composed of two forms of carcinoma that fall into the exactly defined tumor categories of the salivary glands. Carcinomas associated with pleomorphic adenoma include three distinct pathologic entities: carcinoma ex pleomorphic adenoma, carcinosarcoma, and metastasizing pleomorphic adenoma. Unlike these tumors, hybrid carcinomas are composed of two distinct malignant epithelial tumor elements.

Treatment and Prognosis

Of the 18 patients with hybrid carcinoma who were followed up, 1 died of disease, 5 were alive with disease, and 12 were alive with no evidence of disease, although the follow-up period was often short. Several investigators have suggested that the aggressiveness of hybrid carcinomas is determined by the histologically higher-grade element, and the management should be targeted at this tumor component.

K. Intraosseous (Central) Salivary Gland Tumors

Introduction

Salivary gland tumors can rarely develop as intraosseous neoplasms within the mandible and, less commonly, the maxilla. Before a central origin can be accepted, strict exclusion criteria need to be applied. First, there should be no evidence of a primary salivary gland tumor elsewhere. In addition, there should be radiographic evidence of bone destruction within intact cortical plates and a definite diagnosis of a salivary neoplasm (1,2). Proposed origins for these tumors include heterotopic salivary tissue within the maxillofacial skeleton, seromucous glands displaced from the maxillary antrum, and neoplastic transformation of odontogenic rests or cysts (3,4).

Clinical Features

Intraosseous salivary gland tumors form about 3% of all minor gland neoplasms (2). The large majority (~75%) arise in the mandible, where the posterior body and angle are the most common sites. There is a single case report of bilateral intramandibular adenoid cystic carcinoma (5). About a third of cases are found

in association with a radicular cyst or an impacted tooth (1), and these may be mistaken for dental pathology (6,7). There is a wide age distribution (1–85) years, with a mean age of about 50 years (1,4). Many cases are symptomless and are discovered during routine radiographic investigations. The most common presenting complaint is swelling, and other symptoms include pain, paresthesia or anesthesia, loosening or spontaneous avulsion of teeth, discharge, and hemorrhage.

Pathology

The overwhelming majority of central salivary gland tumors are malignant (~95%) (1,4). Mucoepidermoid carcinoma is the most common tumor, forming 64% to 77% of the cases in two major series (1,4). The second most frequent tumor is adenoid cystic carcinoma (11–18%) (8), with smaller numbers of adenocarcinoma NOS (3–4%), carcinoma ex pleomorphic adenoma (3–5%), and acinic cell carcinoma (2–3%). Other rare central malignant salivary gland tumors include hyalinizing clear cell carcinoma (9), epithelial-myoepithelial carcinoma (10), and salivary duct carcinoma (11). Benign tumors, which include pleomorphic adenoma (12), myoepithelioma (13), and monomorphic adenoma, are uncommon and account for about 5% of reported cases (1,4).

Differential Diagnosis

The differential diagnosis of central mucoepidermoid carcinomas includes glandular odontogenic cyst (sialo-odontogenic cyst), clear cell odontogenic carcinoma, calcifying epithelial odontogenic carcinoma, and metastatic renal cell carcinoma. Both mucoepidermoid carcinoma and glandular odontogenic cyst can have cystic components and may have areas showing nonkeratinized squamous epithelium and goblet cells. However, glandular odontogenic cysts lack the intermediate cells that are frequently a predominant component of mucoepidermoid carcinoma and may show characteristic whorled epithelial plaques. In addition, the epithelium lining glandular odontogenic cysts is often columnar or pseudostratified columnar in type and frequently shows luminal blebbing or filiform extensions. Furthermore, although glandular odontogenic cyst is multilocular, it does not show the infiltrative growth pattern of mucoepidermoid carcinoma. In difficult cases, the differential staining of cytokeratin 18 in mucoepidermoid carcinoma and cytokeratin 19 in glandular odontogenic cyst may aid distinction (14,15). The clear cell variant of calcifying epithelial odontogenic tumor usually contains either amyloid or calcospherites or both. Clear cell odontogenic carcinoma and metastatic renal carcinoma do not have a squamous or intermediate cell component and lack evidence of intracellular mucin.

Treatment and Prognosis

Malignant intraosseous salivary gland tumors should be treated by radical surgical excision. The recurrence rate for mucoepidermoid carcinoma following such

treatment was 13% (1). However, this increased to 40% when conservative treatments such as marginal resection or curettage were used (1). The rate of metastatic disease is 9% in mucoepidermoid carcinoma but rises to 50% in adenoid cystic carcinoma.

L. Soft Tissue Tumors

Mesenchymal soft tissue tumors, other than hemato-lymphoid tumors, are uncommon in the salivary glands, accounting for 1.9% to 5% of all salivary gland tumors (1–5). Benign soft tissue tumors occur more commonly than sarcomas, with the ratio varying from 18:1 to 2.4:1 (5). They are observed mainly in the major salivary glands, mostly the parotid gland, and only a few have been described as minor salivary gland in origin. Virtually any entity of benign and malignant soft tissue tumors can originate from the salivary glands, but the frequency may differ according to the tumor types (1–7). Pathologic and biologic features of each tumor are essentially identical to those arising in other sites in the body, with a few exceptions.

Of the 220 cases of benign soft tissue tumors of the salivary glands deposited in the AFIP files, about 40% are vascular tumors, followed by 30% neural tumors, 19% fibrous tumors, and 9% lipomas (2). The most common vascular tumors are hemangiomas, especially the juvenile type in infants (8–10), followed by lymphangiomas. Schwannoma and neurofibroma are the two major neural tumors (Fig. 154), and other rare tumors include extracranial meningioma (2). Among the fibrohistiocytic/myofibroblastic tumor groups, nodular fasciitis, fibrous histiocytoma, fibromatosis, myofibromatosis, fibroma, desmoid tumor, solitary fibrous tumor (Fig. 155) (11,12), and inflammatory pseudotumor (inflammatory myofibroblastic tumors) (13–15) have been described (2). However, the latter two tumors encompass a wide spectrum, ranging from benign to low-grade malignancy, with a risk of local recurrence but no significant metastatic potential. Although lipoma is generally a quite common soft tissue tumor, salivary gland origin is rare, accounting for less than 0.5% of all salivary gland tumors (4). Several microscopic variants of lipoma of the salivary glands, such as angiolipoma, fibrolipoma, pleomorphic lipoma, spindle cell lipoma, and sialolipoma, have been reported (16–19). Miscellaneous other tumors include granular cell tumor (Fig. 156), angio-myoma (vascular leiomyoma), glomangioma, and osteochondroma (2,5).

Salivary gland sarcomas are very rare, accounting for 0.5% of all salivary gland tumors and 1.5% of all salivary gland malignancies (4). Because of their rarity, before making a diagnosis of salivary gland sarcomas, many primary or metastatic neoplasms, such as anaplastic undifferentiated carcinoma, carcinosarcoma, myoepithelial carcinoma, and metastatic malignant melanoma, must first be excluded by careful clinical and pathologic examinations, including extensive immunohistochemical analysis. The 85 cases of salivary gland sarcomas in the AFIP files include hemangiopericytoma, malignant schwannoma (malignant peripheral

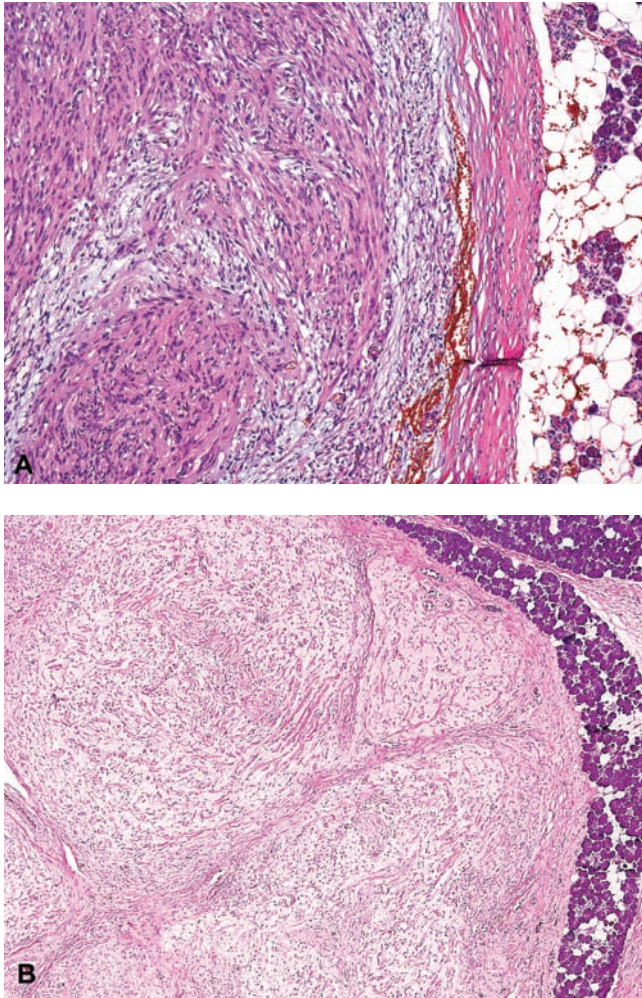


Figure 154 Benign neural tumors arising in the parotid gland. (A) Schwannoma. Encapsulated, well-circumscribed tumor composed of spindle cells arranged in an interlacing fascicular pattern. (B) Neurofibroma. Multilobular appearance of the myxoid tumor is evident. Note the lack of a capsule.

nerve sheath tumor), fibrosarcoma, malignant fibrous histiocytoma (Fig. 157), rhabdomyosarcoma, malignant hemangioendothelioma (angiosarcoma) (20), synovial sarcoma, Kaposi's sarcoma (21), leiomyosarcoma, liposarcoma (22), and alveolar soft part sarcoma, in descending order of frequency (3). However, there is controversy as to whether hemangiopericytoma is a distinct clinicopathologic entity or only represents a histologic pattern, as hemangiopericytoma-like appearance may be observed at least focally in various tumors, including primarily solitary fibrous tumors.

A few examples of epithelioid sarcoma, extraosseous chondrosarcoma, osteosarcoma, angiosarcoma, synovial sarcoma, desmoplastic small round cell tumor, and primitive neuroectodermal tumor have also been described (3,7). Primary salivary gland tumors resembling giant cell tumor of the bone, consisting of mononuclear cells and scattered multinucleated giant cells, are rare but have also been

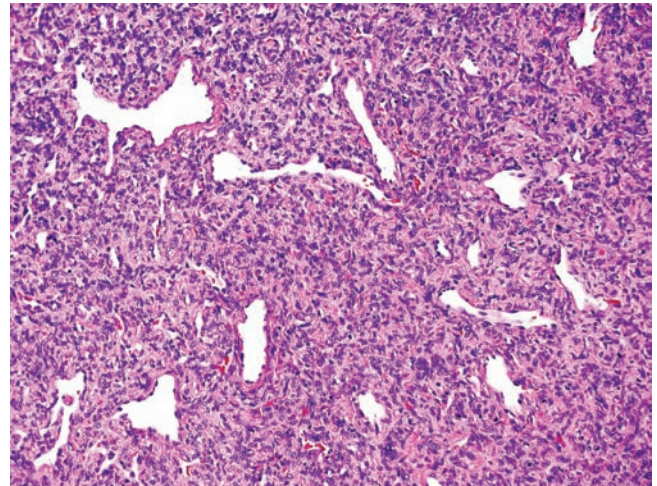


Figure 155 Solitary fibrous tumor arising in the parotid gland. Tumor is composed of haphazardly arranged bland spindle cells and occasional branched hemangiopericytoma-like vessels.

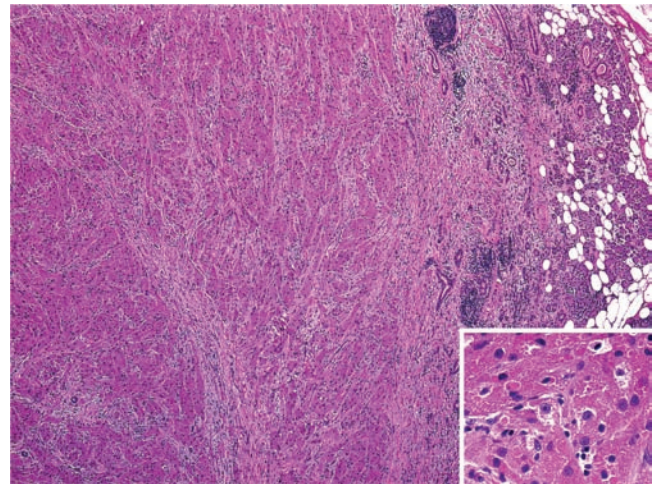


Figure 156 Granular cell tumor arising in the parotid gland. Note the large tumor cells with granular eosinophilic cytoplasm (inset).

reported: 16 such cases can be found in the literature (Fig. 158) (23,24). Nine out of 16 cases (56%) of these salivary giant cell neoplasms were associated with a carcinomatous component. Although it remains to be determined whether giant cell neoplasms are an unusual type of carcinoma or a distinct mesenchymal tumor entity (extraskelatal giant cell tumor of bone), a recent immunohistochemical and genotypical study supports the former hypothesis (23). The age range of salivary sarcomas is from 1 to 93 years, with an average of about 50 years, which is generally older than that of benign soft tissue salivary tumors (23,24).

Many salivary gland sarcomas are high-grade neoplasms; the incidence of local recurrence is 40% to

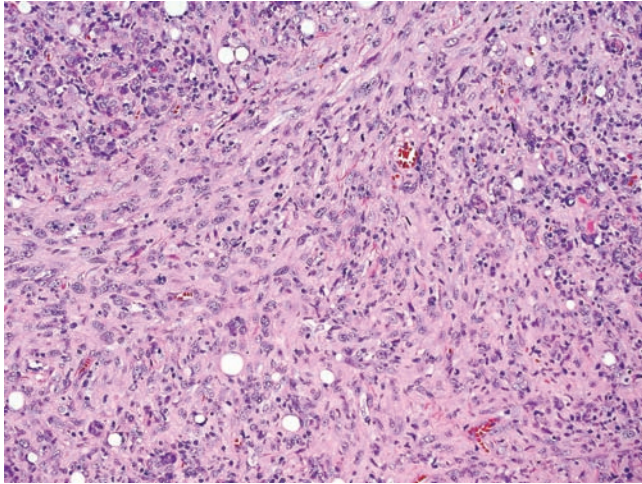


Figure 157 Malignant fibrous histiocytoma involving the parotid gland parenchyma.

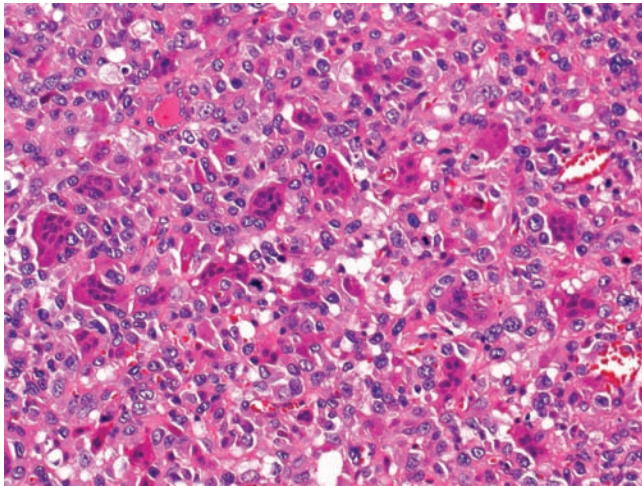


Figure 158 Giant cell tumor arising in the parotid gland. Tumor is composed of round or polygonal mononuclear cells admixed with scattered multinucleated giant cells.

64%, distant metastases occur in 38% to 64%, and the mortality rate is 36% to 64% (6,25). Complete and wide surgical excision is the treatment of choice for salivary gland sarcomas. Postoperative radiation therapy and chemotherapy may improve the outcome.

In this section, two selected benign soft tissue tumors, juvenile hemangioma and sialolipoma, will be discussed. Clinicopathologic details of other soft tissue neoplasms are available elsewhere (Chapter 13).

Juvenile Hemangioma

Introduction. Hemangiomas of the salivary glands are generally divided into capillary and

cavernous types (4,10). Juvenile hemangioma is a histologically immature form of capillary hemangioma and has been previously referred to by various terms, including benign infantile hemangioendothelioma (8), infantile hemangioma, cellular hemangioma of infancy, invasive hemangioma, immature capillary hemangioma, juvenile hemangioma, and congenital capillary hemangioma (9). Juvenile hemangioma is the most common salivary gland tumor in infants.

Clinical features. Juvenile hemangioma occurs at birth or in patients under the age of 12 months, most commonly, in females. This contrasts with the much older patients with average of 26 years and no gender difference in the incidence of cavernous hemangioma (8). Most juvenile hemangiomas involve the parotid gland. Bilateral involvement is found in some patients. Clinically, the patients usually present with a progressively enlarging parotid swelling with no sign of pain or tenderness, giving an erroneous impression of malignancy. The overlying skin may show blue discoloration that is accentuated when the patient cries. Rarely, patients with juvenile hemangioma have been associated with extensive hemangioma development with thrombocytopenia and consumptive coagulopathy known as Kasabach-Merritt syndrome (4).

The majority (75–90%) of juvenile hemangiomas spontaneously involute by the age of seven years (4). In the past, the treatment of juvenile hemangioma was primarily surgical removal of the tumor, including total parotidectomy with sacrifice of the facial nerve. Currently, however, it is recommended to delay operation as long as possible in the hope of seeing spontaneous regression, unless surgical intervention is necessitated by clinical considerations (4). Corticosteroid and interferon therapy may be able to reduce the tumor growth (9).

Pathology. Grossly, the tumor is characteristically composed of many hypertrophic lobules of salivary gland with a gray-reddish color separated by fine connective tissue. In most cases, the basic structure of the parotid gland is maintained, and a tumor mass is indistinct.

Microscopically, the tumor diffusely and uniformly involves the salivary gland lobules (Fig. 159A). The tumor cells produce solid cellular sheets with scattered vascular structures containing a few red blood cells (Fig. 159B). Normal acini and intercalated ducts are widely replaced by tumor cells, leaving only scattered islets of these elements, while striated ducts are well preserved. The tumor consists of two types of cells: endothelial cells and pericytes. The endothelial cells occasionally become plump, with mild nuclear atypia (Fig. 159C). The pericytes are located outside the endothelial basement membrane and have an oval or rounded nucleus with relatively sparse chromatin. Mitotic figures range from rare to moderate in number, but atypical mitoses are never seen. Reticulin fiber staining is helpful in highlighting the small separated cell clusters forming a vascular structure even in a solid cellular area (8).

Immunohistochemically, the endothelial tumor cells of juvenile hemangioma express factor VIII-related antigen, CD31 (Fig. 159D), CD34, and glut-1 (26).

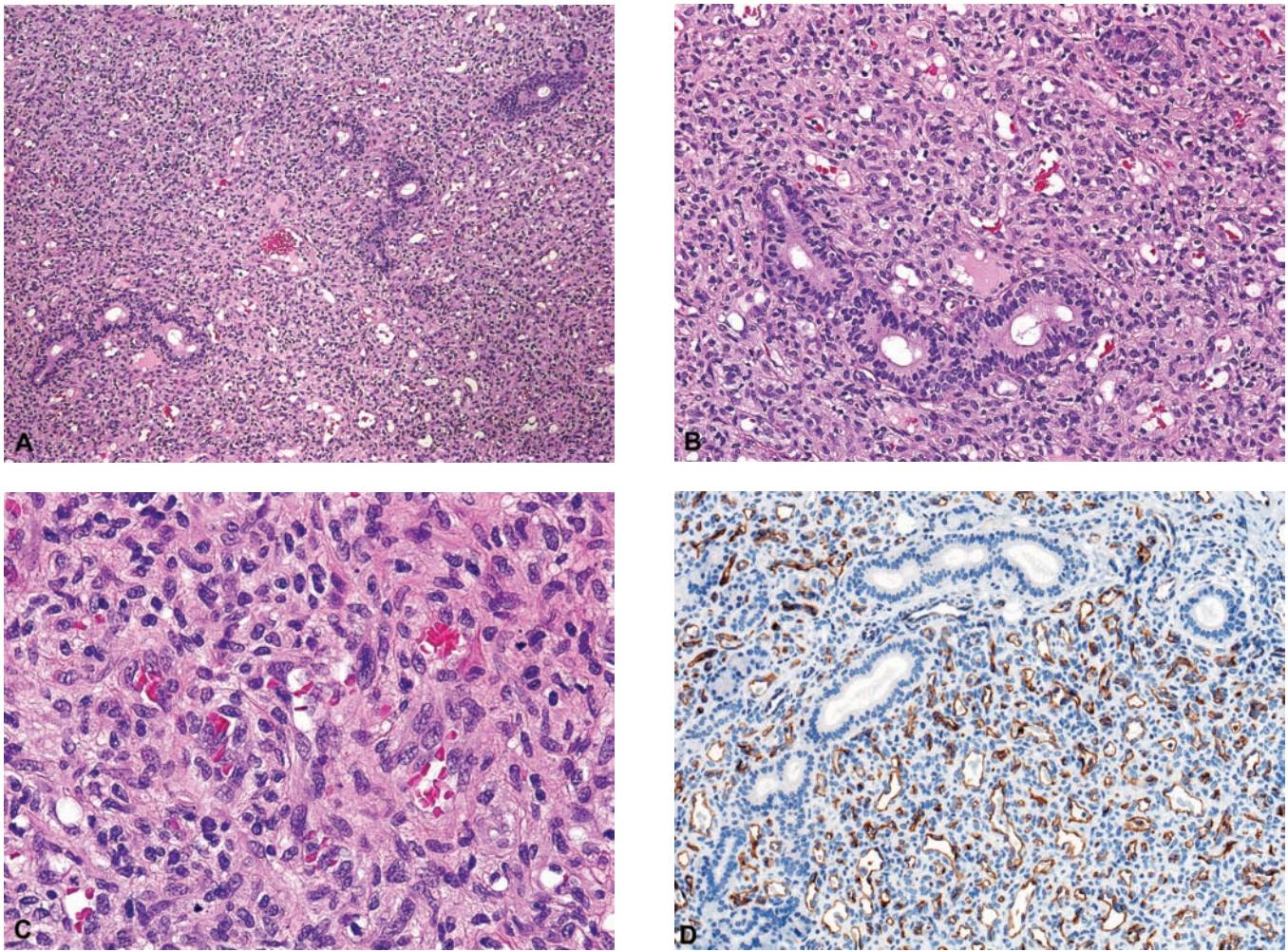


Figure 159 Juvenile hemangioma in the parotid gland. (A) Tumor diffusely and uniformly involves the parotid gland lobules, leaving scattered striated ducts. (B) The tumor cells produce solid cellular nests with scattered vascular structures containing red blood cells. (C) Proliferation of the plump endothelial cells with mild nuclear atypia. (D) Endothelial tumor cells are immunoreactive for CD31.

Differential diagnosis. The most important differential diagnosis of juvenile hemangioma is angiosarcoma. The presence of plump cells in juvenile hemangioma may cause confusion. In angiosarcomas, even in well-differentiated cases, plump cells exhibit more frequent mitotic figures and higher nuclear atypia than juvenile hemangioma. In addition, clinically, angiosarcoma is extremely rare in infants.

Sialolipoma

Introduction. Sialolipoma is a recently described variant of salivary gland lipoma defined by Nagao et al. (19). It is histologically characterized by islands of salivary gland parenchyma enclosed in mature lipomatous tissue.

Clinical features. Sialolipoma is a rare, benign neoplasm; at least 19 cases of a tumor with similar histologic features have been reported (19,27–29). Sialolipomas share similar clinical features with

conventional lipomas of the salivary glands. The patients have been from birth to 84 years old, with an average of 55.7 years except for two congenital cases (19,27–29). Male cases are slightly more common than female ones. It occurs in both major and minor salivary glands. Eleven of the reported tumors arose in the parotid gland, and eight in intraoral minor salivary glands including four involving the palate; one case each occurred in the floor of the mouth, tongue, and buccal mucosa.

Sialolipoma presents as a slow-growing, painless mass with the duration varying from 2 months to 10 years. CT and MRI show a well-circumscribed tumor with a low-intensity CT signal and high-intensity MRI signal. MRI may show scattered or heterogeneous glandular elements. No concurrent history of diabetes mellitus or chronic alcoholism has been reported for any patient with sialolipoma. Superficial parotidectomy or, in the case of minor salivary gland origin, surgical excision is the appropriate treatment for this benign tumor.

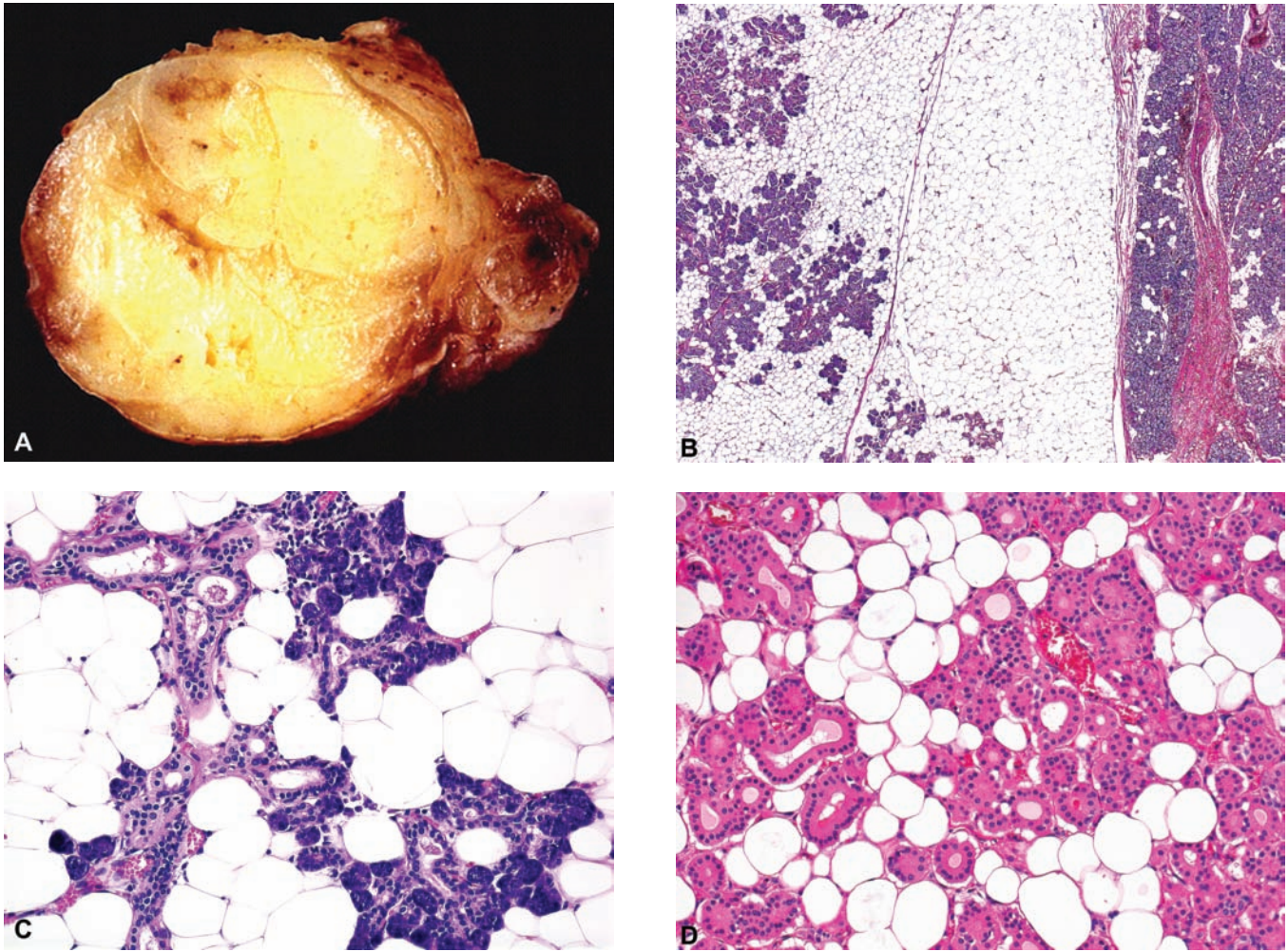


Figure 160 Sialolipoma. (A) A well-circumscribed, yellow mass in the parotid gland. (B) Low-power view showing a tumor sharply separated from the surrounding normal parotid gland tissue. The tumor is composed of mature lipomatous tissue with enclosed islands of salivary gland parenchyma. (C) The glandular components closely resemble the cellular and structural features of a normal salivary gland. (D) Oncocytic change in glandular component.

Pathology. Grossly, sialolipomas are well-circumscribed, soft, and yellow or yellow-white, with a maximum dimension of 1 to 6 cm in the parotid gland (Fig. 160A) and 1 to 3 cm in the minor salivary glands.

Histopathologically, the tumor is a well-circumscribed mass confined by a fibrous capsule and composed of mature adipose tissue and islands of salivary gland parenchymal tissue (Fig. 160B). The amount of fatty tissue in the tumor is higher than that observed in adjacent nontumorous salivary gland tissue. However, the area occupied by the lipomatous component may differ, depending on the site of origin. Tumors in the parotid gland have a greater abundance of adipose tissue, usually constituting 90% or more of the tumor, than those in minor salivary glands.

The glandular component consists of ductal, acinar, basal, and myoepithelial cells without atypia, and closely resembles the cellular and structural features of a normal salivary gland (Fig. 160C), albeit

with some minor variations. The salivary gland parenchymal tissue elements are either distributed sparsely or clustered throughout the tumor. Generally, the glandular components are atrophic. Rarely, a small lymph node, peripheral nerve, or dense lymphoid infiltration is seen at the tumor's periphery. Focal oncocytic (Fig. 160D), sebaceous, and squamous metaplasia may be observed in the glandular component. Occasionally, marked ductal dilatation with fibrosis is evident. Myxoid change can occur in the adipose element. It is likely that the glandular components in sialolipoma become entrapped during lipomatous proliferation, rather than representing true neoplastic elements.

Ultrastructurally, the glandular elements, consisting of ductal, acinar, basal, and myoepithelial cells have features compatible with those observed in the parenchyma of normal parotid gland. The adipose cells have lipid droplets without tonofilaments or myofilaments.

Immunohistochemical studies confirm that the glandular components within the tumor are composed of regularly organized ductal, acinar, and myoepithelial cell elements that have cell-specific phenotypes of normal glands. Focally observed oncocytic cells are strongly immunoreactive for mitochondria. The adipose cells stain positively for S-100 protein. Cell proliferative activity, as assessed by Ki-67 immunostaining, is low.

Differential diagnosis. Several salivary gland conditions or tumors with lipomatous components might be confused with sialolipoma (19). The presence of a fibrous capsule distinguishes sialolipomas from lipomatosis, which constitutes a nontumoral deposition of adipose tissue throughout the gland, resulting in its diffuse enlargement. Lipomatosis may occur in association with diabetes mellitus, liver cirrhosis, chronic alcoholism, malnutrition, and hormonal disturbance, although the exact pathophysiology is still unclear. Unlike lipomatosis, the patients with sialolipoma do not have any of these conditions. In the parotid gland, advancing age is accompanied by acinar atrophy together with the increase in adipose tissue. Sialolipoma, however, shows that the proportion of adipose tissue elements in the tumor is obviously higher than that in nontumorous salivary gland tissue, regardless of age.

Recently, a few case reports of similar tumors have been published; these were categorized as “lipoadenomas” (30) and “oncocytic lipoadenomas” (31). In the former, the glandular tumor components are described as tubules showing a sertoliform pattern without myoepithelial cells and acinar differentiation. Such unique findings are absent, while both myoepithelial and acinar cells are present in sialolipomas. Unlike sialolipomas, the latter tumors are characterized by diffuse oncocytic metaplasia of the glandular elements. In contrast, the metaplastic change is only focally observed, if at all, in sialolipomas. However, since sialolipoma and lipoadenoma share many common histologic features, it is a subject of debate whether these are distinct salivary gland tumors or belong to the same tumor spectrum.

Pleomorphic adenomas rarely contain extensive fatty components, but if these components are present, they may derive from the pluripotential reserve cells of pleomorphic adenoma via a metaplastic process (32). Such a rare variant of pleomorphic adenoma should also be considered in the differential diagnosis of sialolipoma. In sialolipoma, however, the epithelial components are sharply separated from the adipose element. In addition, the presence of normal-appearing acinar cells may exclude the possibility of pleomorphic adenoma.

M. Malignant Lymphomas

Primary salivary gland lymphomas are uncommon, accounting for less than 5% of lymphomas of all sites, 10% of lymphomas arising in the head and neck, and 2% of all salivary gland tumors (1–5). The most common sites of occurrence are the parotid gland,

with approximately 70% of cases, but the submandibular glands and minor salivary glands are also involved in the incidence of 20% to 25% and 5% to 10%, respectively (1). About 10% of the tumors arise in multiple glands (1). Usually, the salivary gland lymphoma presents clinically as a slow-growing salivary gland swelling in a patient over 50 years old.

The majority of the primary salivary gland lymphomas are non-Hodgkin lymphomas of B-cell type; both Hodgkin lymphomas and T-cell lymphomas are extremely rare (5,6). The most common non-Hodgkin lymphomas arising in the salivary glands are extranodal marginal zone B-cell lymphomas (MALT lymphomas), which account for up to 80% of lymphoma cases (5,7). This type of non-Hodgkin lymphoma develops in the setting of acquired lymphoid tissue secondary to long-standing chronic inflammation or, more commonly, to an autoimmune process, such as Sjögren’s syndrome (7–11). Other non-Hodgkin lymphomas involving the salivary glands are usually considered to arise in lymph nodes adjacent to or embedded within the gland and extending into the glandular parenchyma (5). These include follicular lymphoma (Fig. 161), diffuse large B-cell lymphoma, and small lymphocytic lymphoma, with the former two tumors being the most commonly reported, but almost all types of nodal lymphomas can occur (5). It is important to recognize that the natural history and the therapeutic approaches of these nodal-type lymphomas are different from those of MALT lymphoma (5). Diffuse large B-cell lymphomas may develop *de novo* or secondarily by transformation from either MALT lymphoma or follicular lymphoma. Rarely, low-grade lymphomas, in particular, follicular lymphoma, may arise in the lymphoid tissue of Warthin’s tumors (12). The histopathologic features and prognosis of these other non-Hodgkin lymphomas in the salivary glands are identical to those of primary nodal disease of the same type (5).

Comprehensive reviews and textbooks dealing with these fields are currently available elsewhere

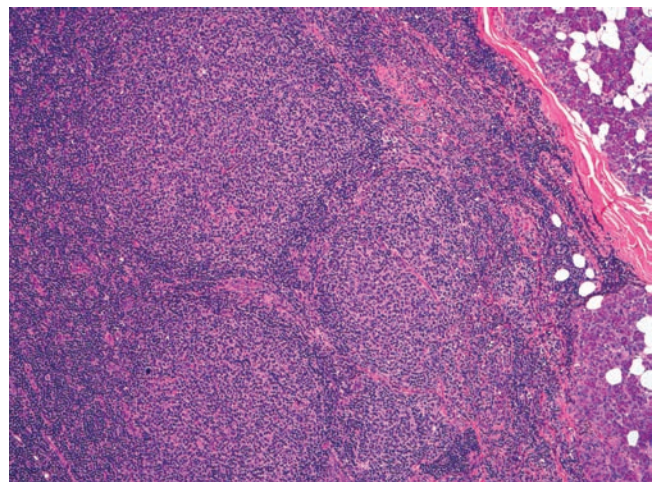


Figure 161 Follicular lymphoma involving the parotid gland.

(5,7,10,13). In this section, only extranodal marginal zone B-cell lymphoma (MALT lymphoma) is discussed.

Extranodal Marginal Zone B-Cell Lymphoma (MALT Lymphoma)

Introduction. Since Isaacson and Wright first described MALT lymphoma of the gastrointestinal tract in 1983 (14), this type of lymphoma has been found in many other organs, such as the salivary gland, thyroid gland, lung, skin, conjunctiva, breast, and larynx (13,15). The salivary gland is the second most common site of involvement of MALT lymphoma following the stomach, which is far more frequently affected, accounting for 70% of all cases (13,15).

The characteristic feature of MALT lymphoma is the proliferation of small- to medium-sized marginal zone cells that infiltrate the ductal epithelium, forming lymphoepithelial lesions. Thus, MALT lymphomas are now definitively considered as extranodal marginal zone B-cell lymphomas (5,9,13). MALT is not normally present in salivary glands, but it may be acquired as a result of chronic inflammatory or autoimmune processes that leads to the pathologic condition referred to as lymphoepithelial sialadenitis (LESA), which was formerly reported as myoepithelial sialadenitis or benign lymphoepithelial lesion. MALT lymphomas usually arise in the context of LESAs in patients with Sjögren's syndrome. The transformation from LESA to MALT lymphoma is postulated to be a multistep process (7,17). Chronic long-term immune stimulation will promote proliferation of the lymphoid cells, and there may be selection or emergence of one or more dominant B-cell clones. Sequentially, sufficient genetic alterations may lead to clonal escape from control of proliferation, and overt lymphoma could eventually develop. Therefore, the monoclonality in itself could be identified in lymphoproliferative disorders with lack of morphologic features of lymphoma (7–10,16–20). These lesions are considered by different authors as pseudolymphomas or prelymphomas, as neoplasms of "uncertain malignant potential" or as early true lymphomas. Various criteria have been utilized to define lymphoma, although none is universally accepted (7–10,16–20). Whatever the event, MALT lymphomas are often localized at presentation and are usually indolent disease entities with a prolonged course; sometimes they involve different anatomic sites and, after some years, may develop into high-grade lymphoma (7,9).

Clinical features. MALT lymphoma usually arises in the patients with a preceding history of LESA induced by an autoimmune disease, most often Sjögren's syndrome. The period of LESA presenting prior to the development of MALT lymphoma varies, ranging from 6 months to 29 years (9). About 4% to 7% of patients with Sjögren's syndrome will develop lymphoma, and the risk of MALT lymphoma in Sjögren's syndrome is 44 times higher than in the normal population (7,10). Development of salivary gland MALT lymphoma has also been described in patients with human immunodeficiency virus and

hepatitis C virus (HCV) infection and in immunocompetent children (7–11). However, the role of hepatitis C virus (HCV) in the pathogenesis of MALT lymphoma remains to be defined (21). Monoclonal gammopathy may be present.

MALT lymphoma occurs predominantly in patients aged 55 to 65 years, with an average of 61 years, mainly in women (5). Most MALT lymphomas arise in the parotid gland, but small numbers of cases have been reported in the submandibular, sublingual, and minor salivary glands (5). Bilateral parotid involvement of MALT lymphoma may occur. The patients typically present with a painless, slowly progressive swelling of the parotid area. The regional lymph nodes may be enlarged because of involvement, but general lymphadenopathy and bone marrow involvement are unusual in MALT lymphoma.

Pathology. Grossly, the tumor presents as an ill-defined, firm mass, yellow to tan on the cut surface. It is usually homogeneous, but microcysts may be observed.

Histologically, the tumor entirely or partially replaces the salivary gland parenchyma by a dense lymphoid infiltrate (Fig. 162), but in either case, lobular structure may be maintained. Features of LESA are usually present. MALT lymphoma is characteristically composed of a diverse range of lymphoid cells with reactive lymphoid follicles and formation of lymphoepithelial lesions. The neoplastic cells infiltrate surrounding reactive secondary lymphoid follicles in a marginal zone distribution and spread outward to form diffuse interfollicular sheets or, in some cases, a vaguely nodular pattern.

The neoplastic lymphoid cells include centrocyte-like (cleaved) cells, monocytoid B cells, small lymphoid cells, lymphoplasmacytic and plasma cells, and large transformed cells in varying numbers. Monocytoid B cells are described as medium-sized cells with lobated or indented nuclei and abundant, pale cytoplasm, often with distinct cell borders. Centrocyte-like cells are slightly smaller cells with less cytoplasm than monocytoid B cells, resembling marginal zone B cells (7). In some cases, plasma cell differentiation may be prominent. In about half of the cases, the neoplastic plasma and lymphoplasmacytic cells may contain PAS-positive Dutcher bodies in their nuclei.

One of the most important histologic hallmarks of MALT lymphoma is the presence of lymphoepithelial lesions, defined by the infiltration and distortion of epithelial structures by aggregates of neoplastic lymphoid cells, usually monocytoid B cells or centrocyte-like cells (Fig. 162C). The affected ducts are often hyperplastic with luminal obliteration or, occasionally, cystic dilatation, causing a multicystic appearance. The early histologic manifestation of the emergence of MALT lymphoma in LESA is the presence of haloes or collars of pale monocytoid B cells and centrocyte-like cells around the epimyoeplithelial islands (lymphoepithelial lesion) (Fig. 162A) (5). Areas of these tumor cells gradually expand and form broad bands, often linking together several lymphoepithelial lesions or diffuse sheets, which eventually replace reactive follicles (Fig. 162B). On the other hand, some reactive

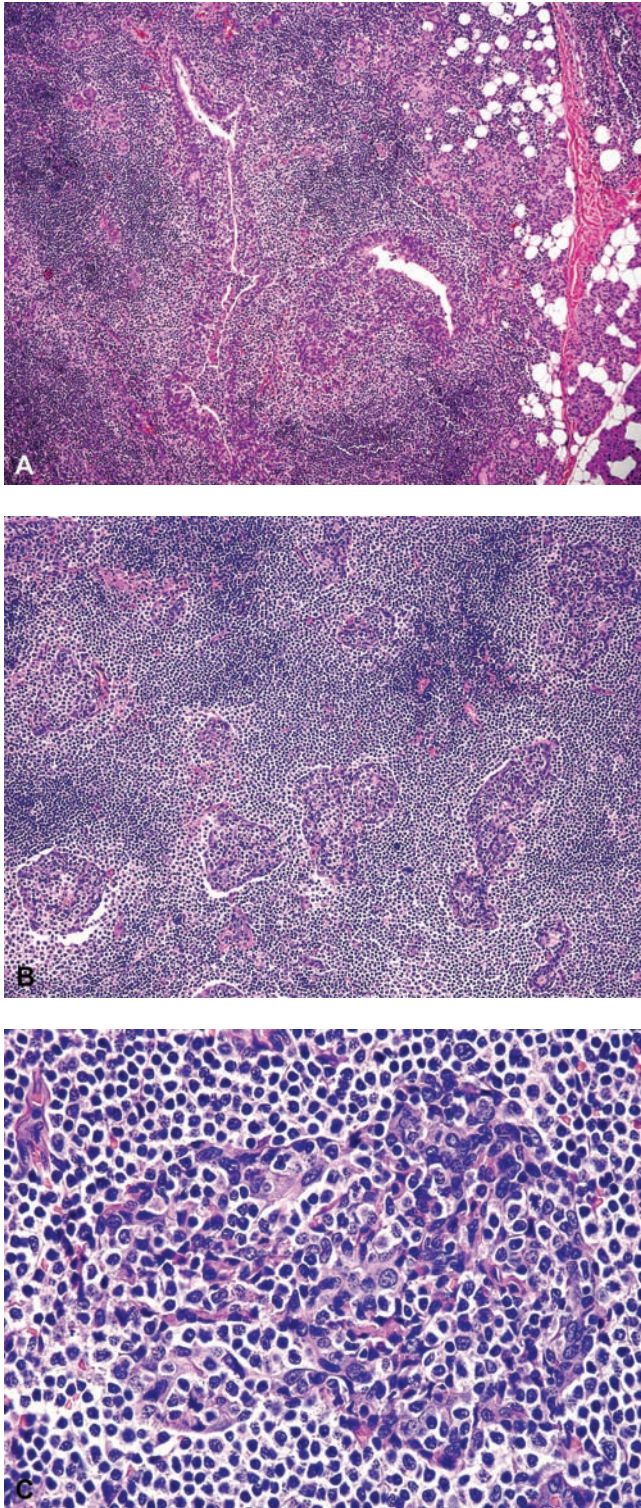


Figure 162 MALT lymphoma. (A) The early stage of MALT lymphoma. Note the presence of haloes or collars of pale monocytoid cells around the lymphoepithelial lesions. (B) The well-developed stage of MALT lymphoma showing scattered lymphoepithelial lesions in diffuse sheets of monocytoid cells. (C) Lymphoepithelial lesion formed by the infiltration of monocytoid cells in the proliferation of duct epithelial cells. *Abbreviation:* MALT, mucosa-associated lymphoid tissue.

follicles may be infiltrated by monocytoid B cells (“follicular colonization”). Additionally, there may be aggregation of epithelioid histiocytes and foci of sclerosis.

Large centroblast- or immunoblast-like cells are typically scattered throughout the tumor. However, in some cases, there are considerably increased numbers of large cells within a typical MALT lymphoma. The exact criteria for the diagnosis of large-cell transformation of MALT lymphoma are not well defined, but the presence of sheets of large transformed cells is thought to represent high-grade transformation (7,9). Although diffuse large B-cell lymphoma can occur de novo or from preexisting MALT lymphoma, with an aggressive behavior, the prognostic significance of the large-cell transformation in MALT lymphoma still remains to be elucidated (7,9). The current WHO classification of tumors of hematopoietic and lymphoid tissues recommends that cases showing transformation to large cell lymphoma should be diagnosed as diffuse large B-cell lymphomas, and the presence of accompanying MALT lymphomas should be noted (13). The term “high-grade MALT lymphoma” is confusing and should be avoided.

Immunohistochemistry. The lymphoid tumor cells of MALT lymphoma express B-cell markers, such as CD19, CD20 (Fig. 163A, left), CD22, and CD79a, but are negative for CD3 (Fig. 163A, right), CD5, CD10, CD23, bcl-6, and cyclin D1 (5,9). Demonstration of immunoglobulin light-chain restriction is helpful to prove the neoplastic nature of the lesion; monotypic immunoglobulin light chain with kappa is seen more often than that with lambda (Fig. 163B) (9). The B cells of MALT lymphoma may be aberrantly positive for CD43 (9). The intrafollicular neoplastic, colonizing B cells are often immunoreactive for bcl-2, but residual, reactive germinal center cells are negative (5). Staining for cytokeratin is useful to reveal lymphoepithelial lesions or scattered epithelial cell remnants.

Differential diagnosis. The differential diagnoses of MALT lymphoma include LESA and certain types of nodal non-Hodgkin lymphomas, such as follicular lymphoma, small lymphocytic lymphoma, and mantle cell lymphoma (5,9).

Distinguishing LESA from MALT lymphoma remains controversial and may be challenging on the basis of histologic examination alone. In such circumstances, immunophenotypic analyses for monoclonality or molecular studies are often required. The presence of haloes of monocytoid B cells surrounding the epimyoepithelial islands (lymphoepithelial lesion) and coalescence of centrocyte-like and monocytoid B cells into broad bands or sheets support the diagnosis of MALT lymphoma rather than LESA. Cytologic atypia, plasma and lymphoplasmacytic cells with Dutcher bodies, and epithelioid histiocytes are associated with lymphoma rather than LESA. Detection of immunoglobulin light-chain restriction by immunohistochemistry or flow cytometry is considered diagnostic of MALT lymphoma. However, LESA may show evidence of oligoclonality or monoclonality revealed by gene rearrangement analysis, suggesting that the monoclonal populations may arise within this process and eventually emerge in the development of

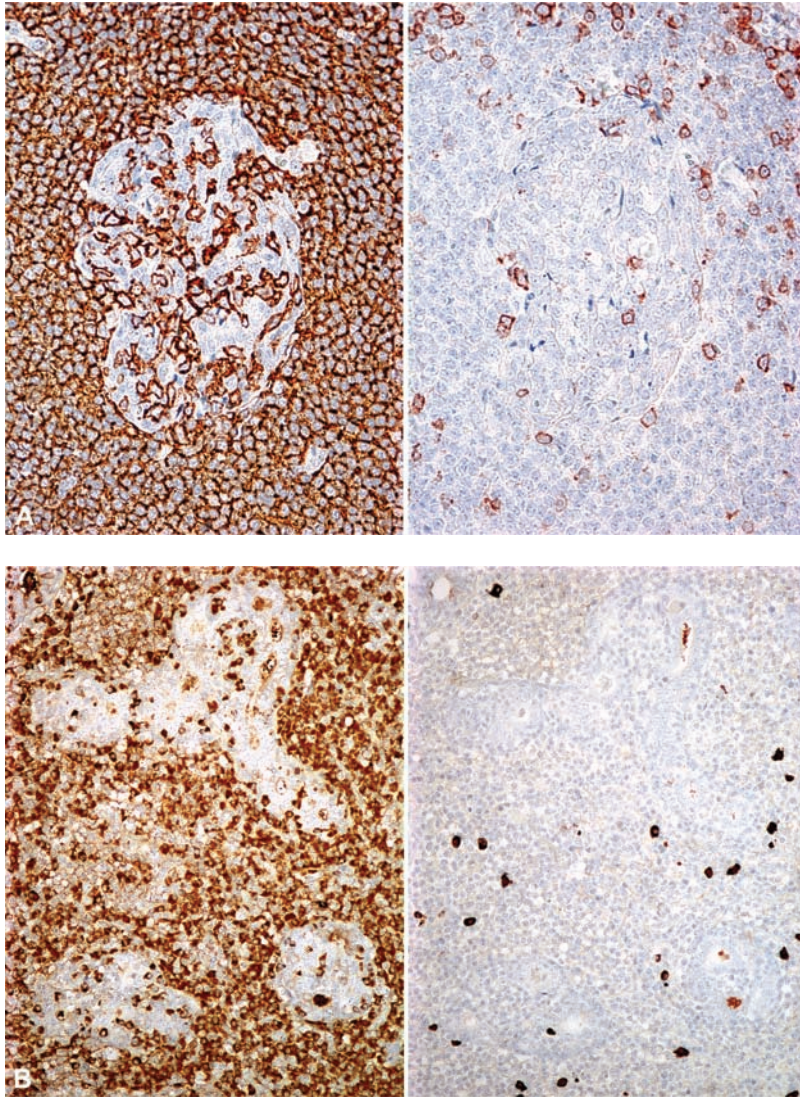


Figure 163 MALT lymphoma. Immunohistochemistry. (A) The lymphoid tumor cells at both inside and outside of the lymphoepithelial lesion diffusely express CD20 (*left*) but are negative for CD3 (*right*). (B) Immunoglobulin light chain restriction. Many kappa light chain-positive cells are seen in the left, whereas only scattered lambda-positive cells are identified in the right. *Abbreviation:* MALT, mucosa-associated lymphoid tissue.

frank lymphoma. Therefore, demonstration of monoclonality by molecular methods is not sufficient to establish a diagnosis of lymphoma. An extensive, dense infiltrate of B cells and aberrant expression of CD43 in the neoplastic B cells are also highly suggestive of lymphoma.

The infiltration of neoplastic B cells into reactive follicles in MALT lymphoma may produce a prominent nodular appearance, leading to confusion with follicular lymphoma. Although both colonized B cells in MALT lymphoma and tumor cells of follicular lymphoma may be positive for *bcl-2*, only the latter express germinal center cell markers, such as CD10 and *bcl-6*. Alternatively, small lymphocytic lymphoma and mantle cell lymphoma are characteristically immunoreactive for CD5 coexpressing CD23 and cyclin D1, respectively, but MALT lymphoma is consistently negative for these markers.

Molecular-genetic data. Monoclonal rearrangements of both heavy- and light-chain immunoglobulin genes are detected in the majority of MALT

lymphomas (7–10,16–20). In the literature, trisomies 3 and 18, and four distinct chromosomal translocations have been demonstrated in MALT lymphoma of various anatomic sites: $t(11;18)(q21;q21)$: *API2-MALT1*, $t(14;18)(q32;q21)$: *IGH-MALT1*, $t(1;14)(p22;q32)$: *BCL10-IGH*, and $t(3;14)(p14.1;q32)$: *IGH-FOXP1* (22–28). These different chromosomal translocations share the final common pathway leading to the activation of nuclear factor- κ B, a transcription factor that regulates the expression of genes associated with lymphocyte proliferation and survival. The specific translocations occur at variable frequencies in MALT lymphomas depending on the sites. The $t(11;18)(q21;q21)$: *API2-MALT1* is the most common chromosomal translocation, found most often in gastric and pulmonary cases but uncommonly in MALT lymphomas of the salivary glands. The $t(14;18)(q32;q21)$: *IGH-MALT1* is found most often in MALT lymphomas arising at nongastric sites including the salivary glands and is identified in approximately 20% of cases. The $t(1;14)(p22;q32)$: *BCL10-IGH* is rarely detected in salivary MALT

lymphomas, resulting in strong aberrant nuclear bcl-10 immunostaining. MALT lymphomas harbor t(3;14) (p14.1;q32): *IGH-FOXP1*—comprising tumors of the thyroid, ocular adnexa, and skin but not those of the salivary glands.

Treatment and prognosis. Most MALT lymphomas have a favorable outcome with five-year survival of 85%, and the tumor usually remains localized to the salivary gland, often for many years (5,9). Lymph node involvement is usually a late event and may involve intraglandular lymph nodes or adjacent cervical lymph nodes. The prognosis of the patients with lymph node involvement is similar to that of primary nodal low-grade B-cell lymphomas. Dissemination to other sites is uncommon in MALT cases, but can include the lung, conjunctiva, or stomach. Typical low-grade MALT lymphoma may undergo transformation into frank diffuse large B-cell lymphoma.

Although the optimal management of MALT lymphoma remains to be established, local treatment with surgical excision, if possible, or radiotherapy seems appropriate. Subsequent chemotherapy may be necessary in case of disseminated disease.

N. Secondary Tumors

Introduction

A secondary tumor of salivary glands is defined as “a metastatic tumor involving salivary glands that originates in a distant site” (1).

Clinical Features

In most large series, metastases account for 1% to 4% of malignant salivary tumors (2). In a recent review, the incidence was 6.5% (3). A major literature review showed that most salivary secondaries involved the parotid gland (~90%), with about 8% affecting the submandibular gland. The peak age of incidence is sixth to eighth decades, with a mean age of about 60 years. Metastases are rare in the pediatric age range. About 80% of secondary tumors in the parotid gland arise from head and neck malignancies (4). The most common sites are the skin of the preauricular area, ear, face, and neck. In the noncutaneous orofacial tissues, the mouth, nasopharynx, and oropharynx are the most frequent sites of primary involvement. Metastases from more distant sites account for about 10% of cases, and lung, kidney, breast, and colorectal tumors form the majority of primary sites. In Gnepp's series, over 15% of cases had an undefined site of origin (2). In the submandibular gland, however, the majority of secondaries are from tumors below the clavicle and result from hematogenous dissemination (2). The most common distant primary sites are the breast, kidney, and lung.

Pathology

It is important for the pathologist to consider the possibility of a secondary tumor when reporting salivary gland neoplasms. Tumors can affect intraparotid

or paraparotid lymph nodes or the salivary gland parenchyma. The most common primary tumors are squamous cell carcinomas and malignant melanomas, which together account for nearly half of parotid metastases. Other relatively less common tumor types include poorly or undifferentiated carcinomas, adenocarcinomas, and carcinomas or malignant tumors (NOS). Metastases from sarcomas and neural malignancies are exceptionally rare. Clear cell carcinomas, including tumors from the kidney and thyroid gland, may be difficult to distinguish from primary salivary neoplasms. The differential diagnosis of clear cell malignancies is discussed in page 562. Some salivary gland tumors, particularly acinic cell carcinoma and mucoepidermoid carcinoma, can have abundant tumor-associated lymphoid proliferation. This should not be interpreted as lymph node metastases (5).

Treatment and Prognosis

Metastatic tumors in the parotid region are often associated with a very poor prognosis, with five-year survival rates of 11.5% and 14.5% for melanoma and squamous cell carcinoma, respectively (6). The prognosis for noncutaneous metastases appears to be even worse (7). In more recent studies, there appears to have been an improvement in the survival rates (8).

REFERENCES

ANATOMY

1. Cheuk W, Chan JK. Advances in salivary gland pathology. *Histopathology* 2007; 51(1):1–20.
2. Ellis GL, Auclair PL. The normal salivary glands. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:20.
3. Tatemoto Y, Kumasa S, Watanabe Y, et al. Epithelial membrane antigen as a marker of human salivary gland acinar and ductal cell function. *Acta Histochem* 1987; 82(2): 219–226.
4. Caselitz J, Seifert G, Jaup T. Presence of carcinoembryonic antigen (CEA) in the normal and inflamed human parotid gland. An immunohistochemical study of 31 cases. *J Cancer Res Clin Oncol* 1981; 100(2):205–211.
5. Prasad AR, Savera AT, Gown AM, et al. The myoepithelial immunophenotype in 135 benign and malignant salivary gland tumors other than pleomorphic adenoma. *Arch Pathol Lab Med* 1999; 123(9):801–806.
6. Simpson RHW. Myoepithelial tumours of the salivary glands. *Curr Diagn Pathol* 2002; 8(5):328–337.
7. Jones H, Moshtael F, Simpson RH. Immunoreactivity of alpha smooth muscle actin in salivary gland tumours: a comparison with S100 protein. *J Clin Pathol* 1992; 45(10): 938–940.
8. Grandi D, Campanini N, Becchi G, et al. On the myoepithelium of human salivary glands. An immunocytochemical study. *Eur J Morphol* 2000; 38(4):249–255.
9. Nakazato Y, Ishida Y, Takahashi K, et al. Immunohistochemical distribution of S-100 protein and glial fibrillary acidic protein in normal and neoplastic salivary glands. *Virchows Arch A Pathol Anat Histopathol* 1985; 405(3): 299–310.

10. Foschini MP, Scarpellini F, Gown AM, et al. Differential expression of myoepithelial markers in salivary, sweat and mammary glands. *Int J Surg Pathol* 2000; 8(1):29–37.
11. Navarro Rde L, Martins MT, de Araújo VC. Maspín expression in normal and neoplastic salivary gland. *J Oral Pathol Med* 2004; 33(7):435–440.
12. Ogawa Y. Immunocytochemistry of myoepithelial cells in the salivary glands. *Prog Histochem Cytochem* 2003; 38(4): 343–426.
13. Bilal H, Handra-Luca A, Bertrand JC, et al. P63 is expressed in basal and myoepithelial cells of human normal and tumor salivary gland tissues. *J Histochem Cytochem* 2003; 51(2):133–139.
14. McKean ME, Lee K, McGregor IA. The distribution of lymph nodes in and around the parotid gland: an anatomical study. *Br J Plast Surg* 1985; 38(1):1–5.
15. Gnepp DR. Sebaceous neoplasms of salivary gland origin: a review. *Pathol Ann Part 1* 1983; 18:71–102.
16. Takeda Y. Melanocytes in the human parotid gland. *Pathol Int* 1997; 47(8):581–583.
- with a review of the literature on heterotopic salivary gland tissue. *J Laryngol Otol* 1976; 90(6):577–584.
8. Cameselle-Teijeiro J, Varela-Durán J. Intrathyroid salivary gland-type tissue in multinodular goiter. *Virchows Arch* 1994; 425(3):331–334.
9. Edwards PC, Bhuiya T, Kahn LB, et al. Salivary heterotopia of the parathyroid gland: a report of two cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99(5):590–593.
10. Curry B, Taylor CW, Fisher AW. Salivary gland heterotopia: a unique cerebellopontine angle tumor. *Arch Pathol Lab Med* 1982; 106(1):35–38.
11. Chen CH, Hsu SS, Lai PH, et al. Intracellular symptomatic salivary gland rest. *J Chin Med Assoc* 2007; 70(5):215–217.
12. Feigin GA, Robinson B, Marchevsky A. Mixed tumor of the mediastinum. *Arch Pathol Lab Med* 1986; 110(1):80–81.
13. Shin CE, Kim SS, Chwals WJ. Salivary gland choristoma of the anterior chest wall. *J Pediatr Surg* 2000; 35(10):1506–1507.
14. Dikman SH, Toker C. Seromucinous gland ectopia within the prostatic stroma. *J Urol* 1973; 109(5):852–854.
15. Marwah S, Berman ML. Ectopic salivary gland in the vulva (choristoma): report of a case and review of the literature. *Obstet Gynecol* 1980; 56(3):389–391.
16. Downs-Kelly E, Hoschar AP, Prayson RA. Salivary gland heterotopia in the rectum. *Ann Diagn Pathol* 2003; 7(2): 124–126.
17. Batsakis JG. Heterotopic and accessory salivary tissues. *Ann Otol Rhinol Laryngol* 1986; 95(4 pt 1):434–435.
18. Batsakis JG. Accessory parotid gland. *Ann Otol Rhinol Laryngol* 1988; 97(4 pt 1):434–435.
19. Youngs LA, Scofield HH. Heterotopic salivary gland tissue in the lower neck. *Arch Pathol* 1967; 83(6):550–556.
20. Lassaletta-Atienza L, López-Ríos F, Martín G, et al. Salivary gland heterotopia in the lower neck: a report of five cases. *Int J Pediatr Otorhinolaryngol* 1998; 43(2):153–161.
21. Haemel A, Gnepp DR, Carlsten J, et al. Heterotopic salivary gland tissue in the neck. *J Am Acad Dermatol* 2008; 58(2):251–256.
22. Hsu RF, Hsu YC, Huang SC. Hereditary ectopic salivary gland: survey of three generations. *Acta Otolaryngol* 2006; 126(3):330–333.
23. Bothra AC, Agarwal RK, Dube MK, et al. Mixed salivary tumor in heterotopic salivary tissue at the base of the neck. *Int Surg* 1977; 62(4):228–229.
24. Ashraf MJ, Azarpira N, Khademi B. Diagnosis of pleomorphic adenoma in a heterotopic salivary gland: a case report. *Acta Cytol* 2007; 51(2):97–99.
25. Singer MI, Applebaum EL, Loy KD. Heterotopic salivary tissue in the neck. *Laryngoscope* 1979; 89(11):1772–1778.
26. Adams WP, Donahoe PK. Salivary gland heterotopia in the lower part of the neck. *Arch Surg* 1979; 114(1):79–81.
27. Himalstein MR. Heterotopic salivary tissue and branchial cleft sinus. *Laryngoscope* 1981; 91(7):1200–1201.
28. Taylor GD, Martin HF. Salivary gland tissue in the middle ear. A rare tumor. *Arch Otolaryngol* 1961; 73:651–653.
29. Namdar I, Smouha EE, Kane P. Salivary gland choristoma of the middle ear: role of intraoperative facial nerve monitoring. *Otolaryngol Head Neck Surg* 1995; 112(4):616–620.
30. Hinni ML, Beatty CW. Salivary gland choristoma of the middle ear: report of a case and review of the literature. *Ear Nose Throat J* 1996; 75(7):422–424.
31. Morimoto N, Ogawa K, Kanzaki J. Salivary gland choristoma in the middle ear: a case report. *Am J Otolaryngol* 1999; 20(4):232–235.
32. Ha SL, Shin JE, Yoon TH. Salivary gland choristoma of the middle ear: a case report. *Am J Otolaryngol* 2000; 21(2): 127–130.

Aplasia, Hypoplasia, Atresia

1. Antoniadis DZ, Markopoulos AK, Deligianni E, et al. Bilateral aplasia of parotid glands correlated with accessory parotid tissue. *J Laryngol Otol* 2006; 120(4):327–329.
2. Milunsky JM, Zhao G, Maher TA, et al. LADD syndrome is caused by FGF10 mutations. *Clin Genet* 2006; 69(4): 349–354.
3. Singh P, Warnakulasuriya S. Aplasia of submandibular salivary glands associated with ectodermal dysplasia. *J Oral Pathol Med* 2004; 33(10):634–636.
4. Codjambopoulo P, Ender-Griepkoven I, Broy H. Bilateral duplication of the submandibular gland and the submandibular duct. *Rofo* 1992; 157(2):185–186.
5. Walker P. Imperforate submandibular duct. *Otolaryngol Head Neck Surg* 2005; 132(4):653–654.
6. Pownell PH, Brown OE, Pransky SM, et al. Congenital abnormalities of the submandibular duct. *Int J Pediatr Otorhinolaryngol* 1992; 24(2):161–169.

Heterotopia

1. Warnock GR, Jensen JL, Kratochvil FJ. Developmental diseases. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:10–14.
2. Goodman RS, Daly JF, Valensi Q. Heterotopic salivary tissue and branchial cleft sinus. *Laryngoscope* 1981; 91(2):260–264.
3. Bouquot JE, Gnepp DR, Dardick I, et al. Intraosseous salivary tissue: jawbone examples of choristomas, hamartomas, embryonic rests, and inflammatory entrapment: another histogenetic source for intraosseous adenocarcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90(2):205–217.
4. Brannon RB, Houston GD, Wampler HW. Gingival salivary gland choristoma. *Oral Surg Oral Med Oral Pathol* 1986; 61(2):185–188.
5. Ledesma-Montes C, Fernández-López R, Garcés-Ortiz M, et al. Gingival salivary gland choristoma. A case report. *J Periodontol* 1998; 69(10):1164–1166.
6. Braun GA, Lowry LD, Meyers A. Bilateral choristomas of the external auditory canals. *Arch Otolaryngol* 1978; 104(8): 467–470.
7. Pesavento G, Ferlito A. Benign mixed tumour of heterotopic salivary gland tissue in upper neck. Report of a case

33. Ookouchi Y, Honda N, Gyo K. Salivary gland choristoma of the middle ear in a child: a case report. *Otolaryngol Head Neck Surg* 2003; 128(1):160–162.
34. Rinaldo A, Ferlito A, Devaney KO. Salivary gland choristoma of the middle ear. A review. *ORL J Otorhinolaryngol Relat Spec* 2004; 66(3):141–147.
35. Enoz M, Suoglu Y. Salivary gland choristoma of the middle ear. *Laryngoscope* 2006; 116(6):1033–1034.
36. Caplinger CB, Hora JF. Middle ear choristoma with absent oval window. A report of one case. *Arch Otolaryngol* 1967; 85(4):365–366.
37. Peron DL, Schuknecht HF. Congenital cholesteatomata with other anomalies. *Arch Otolaryngol* 1975; 101(8):498–505.
38. Saeed YM, Bassis ML. Mixed tumor of the middle ear. A case report. *Arch Otolaryngol* 1971; 93(4):433–434.
39. Peters BR, Maddox HE III, Batsakis JG. Pleomorphic adenoma of the middle ear and mastoid with posterior fossa extension. *Arch Otolaryngol Head Neck Surg* 1988; 114(6):676–678.
40. Quaranta A, Mininni F, Resta L. Salivary gland choristoma of the middle ear: a case report. *J Laryngol Otol* 1981; 95(9):953–956.
41. Saeger KL, Gruskin P, Carberry JN. Salivary gland choristoma of the middle ear. *Arch Pathol Lab Med* 1982; 106(1):39–40.
42. Abadir WF, Pease WS. Salivary gland choristoma of the middle ear. *J Laryngol Otol* 1978; 92(3):247–252.
43. Hanson JR, Anson BJ, Strickland EM. Branchial sources of the auditory ossicles in man. II. Observations of embryonic stages from 7 mm. to 28 mm. (CR length). *Arch Otolaryngol* 1962; 76:200–215.
44. Correll RW, Jensen JL, Rhyne RR. Lingual cortical mandibular defects: a radiographic incidence study. *Oral Surg Oral Med Oral Pathol* 1980; 50(3):287–291.
45. Stafne EC. Bone cavities situated near the angle of the mandible. *J Am Dent Assoc* 1942; 29:1969–1972.
46. Lello GE, Makek M. Stafne's mandibular lingual cortical defect. Discussion of aetiology. *J Maxillofac Surg* 1985; 13(4):172–176.
47. Uemura S, Fujishita M, Fuchihata H. Radiographic interpretation of so-called developmental defect of mandible. *Oral Surg Oral Med Oral Pathol* 1976; 41(1):120–128.
48. Shimizu M, Osa N, Okamura K, et al. CT analysis of the Stafne's bone defects of the mandible. *Dentomaxillofac Radiol* 2006; 35(2):95–102.
49. Choukas NC, Toto PD. Etiology of static bone defects of the mandible. *J Oral Surg Anesth Hosp Dent Serv* 1960; 18:16–20.
50. Shear M, Speight PM. Cysts of the Oral and Maxillofacial Regions. 4th ed. Oxford: Blackwell Munksgaard, 2007: 160–161.
51. Buchner A, Carpenter WM, Merrell PW, et al. Anterior lingual mandibular salivary gland defect. Evaluation of twenty-four cases. *Oral Surg Oral Med Oral Pathol* 1991; 71(2):131–136.
52. Dorman M, Pierse D. Ectopic salivary gland tissue in the anterior mandible: a case report. *Br Dent J* 2002; 193(10):571–572.
53. de Courten A, Küffer R, Samson J, et al. Anterior lingual mandibular salivary gland defect (Stafne defect) presenting as a residual cyst. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 94(4):460–464.
- differential diagnosis of a rare disease of the salivary glands. *Virchows Arch A Pathol Anat Histol* 1981; 390(3): 273–288.
2. Dobson CM, Ellis HA. Polycystic disease of the parotid glands: case report of a rare entity and review of the literature. *Histopathology* 1987; 11(9):953–961.
3. Batsakis JG, Bruner JM, Luna MA. Polycystic (dysgenetic) disease of the parotid glands. *Arch Otolaryngol Head Neck Surg* 1988; 114(10):1146–1148.
4. Smyth AG, Ward-Booth RP, High AS. Polycystic disease of the parotid glands: two familial cases. *Br J Oral Maxillofac Surg* 1993; 3(1):38–40.
5. Garcia S, Martini F, Caces F, et al. Polycystic disease of the salivary glands: report of an attack of the submaxillary glands. (Article in French) *Ann Pathol* 1998; 18(1):58–60.

Cystic Fibrosis (Mucoviscidosis)

1. Mandel ID, Kutscher A, Denning CR, et al. Salivary studies in cystic fibrosis. *Am J Dis Child* 1967; 113(4):431–438.
2. Doggett RG, Bentinck B, Harrison GM. Structure and ultrastructure of the labial salivary glands in patients with cystic fibrosis. *J Clin Pathol* 1971; 24(3):270–282.
3. Tandler B. Salivary gland changes in disease. *J Dent Res* 1987; 66(2):398–406.
4. Davis PB. Pathophysiology of cystic fibrosis with emphasis on salivary gland involvement. *J Dent Res* 1987; 66 Spec No, 667–671.

Sebaceous Glands

1. Martinez-Madriral F, Micheau C. Histology of the major salivary glands. *Am J Surg Pathol* 1989; 13(10):879–899.
2. Linhartova A. Sebaceous glands in salivary gland tissue. *Arch Pathol* 1974; 98(5):320–324.
3. Gnepp DR. Sebaceous neoplasms of salivary gland origin: a review. *Pathol Ann Part 1* 1983; 18:71–102.
4. Meza-Chávez L. Sebaceous glands in normal and neoplastic parotid glands. *Am J Pathol* 1949; 98:627–645.
5. Batsakis JG, el-Naggar AK. Sebaceous lesions of salivary glands and oral cavity. *Ann Otol Rhinol Laryngol* 1990; 99(5):416–418.

Salivary Gland Cysts

1. Kundu S, Cheng J, Maruyama S, et al. Lymphatic involvement in the histopathogenesis of mucous retention cyst. *Pathol Res Pract* 2007; 203(2):89–97.
2. Shear M, Speight PM. Cysts of the Oral and Maxillofacial Regions. 4th ed. Oxford: Blackwell Munksgaard, 2007: 171–180.
3. Porter SR, Scully C, Kainth B, et al. Multiple salivary mucocles in a young boy. *Int J Paediatr Dent* 1998; 8(2):149–151.
4. Southam JC. Retention mucocles of the oral mucosa. *J Oral Pathol* 1974; 3(4):197–202.
5. Eversole LR. Oral sialocysts. *Arch Otolaryngol Head Neck Surg* 1987; 113(1):51–56.
6. Eveson JW. Superficial mucocles: pitfall in clinical and microscopic diagnosis. *Oral Surg Oral Med Oral Pathol* 1988; 66(3):318–322.
7. Campana F, Sibaud V, Chauvel A, et al. Recurrent superficial mucocles associated with lichenoid disorders. *J Oral Maxillofac Surg* 2006; 64(12):1830–1833.
8. Garcia-F-Villalta MJ, Pascual-Lopez M, Elices M, et al. Superficial mucocles and lichenoid graft versus host disease: report of three cases. *Acta Derm Venereol* 2002; 82(6):453–455.
9. Richardson GS, Clairmont AA, Erickson ER. Cystic lesions of the parotid gland. *Plast Reconstr Surg* 1978; 61(2):364–370.

Polycystic (Dysgenetic) Disease

1. Seifert G, Thomsen S, Donath K. Bilateral dysgenetic polycystic parotid glands. Morphological analysis and

10. Chaudhry AP, Yamane GM, Scharlock SE, et al. A clinicopathological study of intraoral lymphoepithelial cysts. *J Oral Med* 1984; 39(4):79–84.
11. Buchner A, Hansen LS. Lymphoepithelial cysts of the oral cavity. A clinicopathologic study of thirty-eight cases. *Oral Surg Oral Med Oral Pathol* 1980; 50(5):441–449.
12. Olsen KD, Maragos NE, Weiland LH. First branchial cleft anomalies. *Laryngoscope* 1980; 90(3):423–436.
13. Bernier JL, Bhaskar SN. Lymphoepithelial lesions of salivary glands. *Cancer* 1958; 11(6):1156–1178.
14. Cleary KR, Batsakis JG. Lymphoepithelial cysts of the parotid region: a “new face” on an old lesion. *Ann Otol Rhinol Laryngol* 1990; 99(2 pt 1):162–164.
15. Gnepp DR, Sporck FT. Benign lymphoepithelial parotid cyst with sebaceous differentiation—cystic sebaceous lymphadenoma. *Am J Clin Pathol* 1980; 74(5):683–687.
16. Pieterse AS, Seymour AE. Parotid cysts. An analysis of 16 cases and suggested classification. *Pathology* 1981; 13(2):225–234.

Infiltration

Lipomatosis

1. Izumi M, Eguchi K, Nakamura H, et al. Premature fat deposition in the salivary glands associated with Sjögren syndrome: MR and CT evidence. *AJNR Am J Neuroradiol* 1997; 18(5):951–958.
2. Seifert G. Lipomatous cystic pancreas fibrosis and lipomatous pancreas atrophy in childhood. *Beitr Pathol Anat* 1959; 121:64–80.
3. Al-Arfaj AA, Arora RK, El Hassan AY, et al. Lipomatosis of the parotid gland in children. *Saudi Med J* 2003; 24(8):898–900.
4. Saleh HA, Ram B, Harmse JL, et al. Lipomatosis of the minor salivary glands. *J Laryngol Otol* 1998; 112(9):895–897.

Oncocytic Lesions

1. Hamperl H. Das Onkocytom der Speicheldrüsen. *Z Krebsforsch* 1962; 64:427–440.
2. Shintaku M, Honda T. Identification of oncocytic lesions of salivary glands by anti-mitochondrial immunohistochemistry. *Histopathology* 1997; 31(5):408–411.
3. Johns ME, Regezi JA, Batsakis JG. Oncocytic neoplasms of salivary glands: an ultrastructural study. *Laryngoscope* 1977; 87(6):262–271.
4. Capone RB, Ha PK, Westra WH, et al. Oncocytic neoplasms of the parotid gland: a 16-year institutional review. *Otolaryngol Head Neck Surg* 2002; 126(6):657–662.
5. Batsakis JG, Regezi JA. Selected controversial lesions of salivary tissues. *Otolaryngol Clin North Am* 1977; 10(2):309–328.
6. Meza-Chavel L. Oxyphilic granular cell adenoma of the parotid gland (oncocytoma). Report of five cases and study of oxyphilic granular cells (oncocytes) in normal parotid glands. *Am J Pathol* 1949; 25:523–538.
7. Vigliani R, Genetta C. Diffuse hyperplastic oncocytosis of the parotid gland. Case report with histochemical observations. *Virchows Arch Pathol Anat* 1982; 397(2):235–240.
8. Schwartz IS, Feldman M. Diffuse multinodular oncocytoma (“oncocytosis”) of the parotid gland. *Cancer* 1969; 23(3):636–640.
9. Loreti A, Sturla M, Gentileschi S, et al. Diffuse hyperplastic oncocytosis of the parotid gland. *Br J Plast Surg* 2002; 55(2):151–152.

10. Mandel L, Carrao V. Bilateral parotid diffuse hyperplastic oncocytosis: case report. *J Oral Maxillofac Surg* 2005; 63(4):560–562.
11. Palmer TJ, Gleeson MJ, Eveson JW, et al. Oncocytic adenomas and oncocytic hyperplasia of salivary glands: a clinicopathological study of 26 cases. *Histopathology* 1990; 16(5):487–493.
12. Srensen M, Baunsgaard P, Frederiksen P, et al. Multifocal adenomatous oncocytic hyperplasia of the parotid gland. (Unusual clear cell variant in two female siblings.) *Pathol Res Pract* 1986; 181(2):254–257.
13. Brandwein MS, Huvois AG. Oncocytic tumors of major salivary glands. A study of 68 cases with follow-up of 44 patients. *Am J Surg Pathol* 1991; 15(6):514–528.
14. Hartwick RW, Batsakis JG. Non-Warthin’s tumor oncocytic lesions. *Ann Otol Rhinol Laryngol* 1990; 99(8):674–677.

Amyloidosis

1. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. *Mayo Clin Proc* 1983; 58(10):665–683.
2. Browning MJ, Banks RA, Tribe CR, et al. Ten years experience of an amyloid clinic—a clinicopathological survey. *Q J Med* 1985; 54(215):213–227.
3. Stimson PG, Tortoledo ME, Luna MA, et al. Localized primary amyloid tumor of the parotid gland. *Oral Surg Oral Med Oral Pathol* 1988; 66(4):466–469.
4. Mateo Arias J, Molina Martinez M, Borrego A, et al. Amyloidosis of the submaxillary gland. *Med Oral* 2003; 8(1):66–70.
5. Kurokawa H, Takuma C, Tokudome S, et al. Primary localization amyloidosis of the sublingual gland. *Fukuoka Igaku Zasshi* 1998; 89(7):216–220.
6. Ustün MO, Ekinci N, Payzin B. Extramedullary plasmacytoma of the parotid gland. Report of a case with extensive amyloid deposition masking the cytologic and histopathologic picture. *Acta Cytol* 2001; 45(3):449–453.
7. Jardinet D, Westhovens R, Peeters J. Sicca syndrome as an initial symptom of amyloidosis. *Clin Rheumatol* 1998; 17(6):546–548.
8. Delèvaux I, André M, Amoura Z, et al. Concomitant diagnosis of primary Sjögren’s syndrome and systemic AL amyloidosis. *Ann Rheum Dis* 2001; 60(7):694–695.
9. Delgado WA, Mosqueda A. A highly sensitive method for diagnosis of secondary amyloidosis by labial salivary gland biopsy. *J Oral Pathol Med* 1989; 18(5):310–314.
10. Hachulla E, Janin A, Flipo RM, et al. Labial salivary gland biopsy is a reliable test for the diagnosis of primary and secondary amyloidosis. A prospective clinical and immunohistologic study in 59 patients. *Arthritis Rheum* 1993; 36(5):691–697.

Iron Deposition

1. Blandford RL, Dowdle JR, Stephens MR, et al. Sicca syndrome associated with idiopathic haemochromatosis. *Br Med J* 1979; 1(6174):1323.
2. Ward-Booth P, Ferguson MM, MacDonald DG. Salivary gland involvement in hemochromatosis. *Oral Surg Oral Med Oral Pathol* 1981; 51(5):487–488.
3. Takeda Y, Ohya T. Sicca symptom in a patient with hemochromatosis: minor salivary gland biopsy for differential diagnosis. *Int J Oral Maxillofac Surg* 1987; 16(6):745–748.
4. Goldfarb A, Nitzan DW, Marmary Y. Changes in the parotid salivary gland of beta-thalassemia patients due to hemosiderin deposits. *Int J Oral Surg* 1983; 12(2):115–119.
5. Borgna-Pignatti C, Cammareri V, De Stefano P, et al. The sicca syndrome in thalassaemia major. *Br Med J (Clin Res Ed)* 1984; 288(6418):668–669.

6. Vaiopoulos G, Konstantopoulos K, Kittas C, et al. Histological and functional changes in the salivary glands in thalassaemia major. *Haematologia (Budap)* 1995; 27(1): 33–38.
7. Smith SR, Shneider BL, Magid M, et al. Minor salivary gland biopsy in neonatal hemochromatosis. *Arch Otolaryngol Head Neck Surg* 2004; 130(6):760–763.

Sialadenitis

Acute Suppurative Sialadenitis

1. Krippaehne WW, Hunt TK, Dunphy JE. Acute suppurative parotitis: a study of 161 cases. *Ann Surg* 1962; 156(2): 251–257.
2. Brook I. Diagnosis and management of parotitis. *Arch Otolaryngol Head Neck Surg* 1992; 118(5):469–471.
3. McQuone SJ. Acute viral and bacterial infections of the salivary glands. *Otolaryngol Clin North Am* 1999; 32(5): 793–811.
4. Brooke I. Acute bacterial suppurative parotitis: microbiology and management. *J Craniofac Surg* 2003; 14(1):37–40.
5. Malloy KM, Rosen DR, Rosen MR. Sialadenitis. In: Witt RL ed. *Salivary Gland Diseases: Surgical and Medical Management*. New York: Thieme Medical Publishers Inc, 2005:54–70.

Obstructive Sialadenitis and Sialolithiasis

1. Koudelka BM. Obstructive disorders. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:26–38.
2. Seifert G. Aetiological and histological classification of sialadenitis. *Pathologica* 1997; 89(1):7–17.
3. Marchal F, Dulguerov P. Sialolithiasis management: the state of the art. *Arch Otolaryngol Head Neck Surg* 2003; 129(9):951–956.
4. Harrison JD. Histology and Pathology of Sialolithiasis. In: Witt RL, ed. *Salivary Gland Diseases: Surgical and Medical Management*. New York: Thieme Medical Publishers, Inc., 2005:71–78.
5. Peel RL. Diseases of the salivary gland. In: Barnes L, ed. *Surgical Pathology of the Head and Neck*. New York: Marcel Dekker Inc, 2001:633–758.
6. Iro H, Dlugaczky J, Zenk J. Current concepts in diagnosis and treatment of sialolithiasis. *Br J Hosp Med (Lond)* 2006; 67(1):24–28.
7. Isacson G, Ahlner B, Lundquist PG. Chronic sialadenitis of the submandibular gland. A retrospective study of 108 cases. *Arch Otorhinolaryngol* 1981; 232(1):91–100.
8. Marchal F, Kurt AM, Dulguerov P, et al. Histopathology of submandibular glands removed for sialolithiasis. *Ann Otol Rhinol Laryngol* 2001; 110(5 pt 1):464–469.
9. Teymoortash A, Tiemann M, Schrader C, et al. Characterization of lymphoid infiltrates in chronic obstructive sialadenitis associated with sialolithiasis. *J Oral Pathol Med* 2004; 33(5):300–304.

Chronic Sclerosing Sialadenitis (Küttner Tumor)

1. Küttner H. Über entzündliche Tumoren der Submaxillarspeicheldrüse. *Bruns Beitr Klin Chir* 1896; 15:815–828.
2. Chan JKC. Küttner tumor (chronic sclerosing sialadenitis) of the submandibular gland: an underrecognized entity. *Adv Anat Pathol* 1998; 5(4):239–251.
3. Ellis GL, Auclair PL. Chronic sclerosing sialadenitis. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*,

3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:419–421.

4. Harrison JD, Epivatianos A, Bhatia SN. Role of microliths in the aetiology of chronic submandibular sialadenitis: a clinicopathological investigation of 154 cases. *Histopathology* 1997; 31(3):237–251.
5. Seifert G, Donath K. On the pathogenesis of the Küttner tumor of the submandibular gland: analysis of 349 cases with chronic sialadenitis of the submandibular gland. *HNO* 1977; 25(3):81–92.
6. Tiemann M, Teymoortash A, Schrader C, et al. Chronic sclerosing sialadenitis of the submandibular gland is mainly due to a T lymphocyte immune reaction. *Mod Pathol* 2002; 15(8):845–852.
7. Kitagawa S, Zen Y, Harada K, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am J Surg Pathol* 2005; 29(6):783–791.
8. Kamisawa T, Nakajima H, Hishima T. Close correlation between chronic sclerosing sialadenitis and immunoglobulin G4. *Intern Med J* 2006; 36(8):527–529.
9. Kamisawa T, Nakajima H, Egawa N, et al. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatol* 2006; 6(1–2):132–137.
10. Tanabe T, Tsushima K, Yasuo M, et al. IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. *Intern Med* 2006; 45(21): 1243–1247.
11. Cheuk W, Yuen HK, Chu SY, et al. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol* 2008; 32(5):671–681.
12. Blanco M, Mesko T, Cura M, et al. Chronic sclerosing sialadenitis (Küttner's tumor): unusual presentation with bilateral involvement of major and minor salivary glands. *Ann Diagn Pathol* 2003; 7(1):25–30.
13. Ochoa ER, Harris NL, Pilch BZ. Marginal zone B-cell lymphoma of the salivary gland arising in chronic sclerosing sialadenitis (Küttner tumor). *Am J Surg Pathol* 2001; 25(12):1546–1550.
14. Van der Walt JD, Leake J. Granulomatous sialadenitis of the major salivary glands. A clinicopathological study of 57 cases. *Histopathology* 1987; 11(2):131–144.
15. Seifert G. Tumour-like lesions of the salivary glands. The new WHO classification. *Pathol Res Pract* 1992; 188(7): 836–846.
16. Kojima M, Nakamura S, Itoh H, et al. Küttner's tumor of salivary glands resembling marginal zone B-cell lymphoma of the MALT type: a histopathologic and immunohistochemical study of 7 cases. *Int J Surg Pathol* 2004; 12(4): 389–393.
17. Kojima M, Nakamura S, Itoh H. Sclerosing variant of follicular lymphoma arising from submandibular glands and resembling "Küttner tumor": a report of 3 patients. *Int J Surg Pathol* 2003; 11(4):303–307.

Radiation Sialadenitis

1. Vokes EE, Weichselbaum RR, Lippman SM, et al. Head and neck cancer. *N Engl J Med* 1993; 328(3):184–194.
2. Bansal M, Mohanti BK, Shah N, et al. Radiation related morbidities and their impact on quality of life in head and neck cancer patients receiving radical radiotherapy. *Qual Life Res* 2004; 13(2):481–488.
3. Mossman KL, Shatzman AR, Chencharick JD. Effects of radiotherapy on human parotid saliva. *Radiat Res* 1981; 88(2):403–412.

4. Stephens LC, King GK, Peters LJ, et al. Acute and late radiation injury in rhesus monkey parotid glands. Evidence of interphase cell death. *Am J Pathol* 1986; 124(3): 469–478.
5. Stephens LC, King GK, Peters LJ, et al. Unique radiosensitivity of serous cells in rhesus monkey submandibular glands. *Am J Pathol* 1986; 124(3):479–487.
6. Nagler RM. Effects of head and neck radiotherapy on major salivary glands—animal studies and human implications. *In Vivo* 2003; 17(4):369–375.
7. Dreyer JO, Sakuma Y, Seifert G. (Radiation-induced sialadenitis. Stage classification and immunohistology) *Pathologie* 1989; 10(3):165–170.
8. Teymoortash A, Simolka N, Schrader C, et al. Lymphocyte subsets in irradiation-induced sialadenitis of the submandibular gland. *Histopathology* 2005; 47(5):493–500.

Cheilitis Glandularis

1. von Volkman R. Eine Falle von Cheilitis Glandularis Apostematosa (Myxadenitis Labialis). *Virchows Arch Pathol Anat [A]* 1870; 50:142–144.
2. Michalowski R. Cheilitis glandularis, heterotopic salivary glands and squamous cell carcinoma of the lip. *Br J Dermatol* 1962; 74:445–449.
3. Doku HC, Shklar G, McCarthy PL. Cheilitis glandularis. *Oral Surg Oral Med Oral Pathol* 1965; 20(5):563–571.
4. Weir TW, Johnson WC. Cheilitis glandularis. *Arch Dermatol* 1971; 103(4):433–437.
5. Oliver ID, Pickett AB. Cheilitis glandularis. *Oral Surg Oral Med Oral Pathol* 1980; 49(6):526–529.
6. Stuller CB, Schaberg SJ, Stokos J, et al. Cheilitis glandularis. *Oral Surg Oral Med Oral Pathol* 1982; 53(6):602–605.
7. Swerlick RA, Cooper PH. Cheilitis glandularis: a re-evaluation. *J Am Acad Dermatol* 1984; 10(3):466–472.
8. Winchester L, Scully C, Prime SS, et al. Cheilitis glandularis: a case affecting the upper lip. *Oral Surg Oral Med Oral Pathol* 1986; 62(6):654–656.
9. Yacobi R, Brown DA. Cheilitis glandularis: a pediatric case report. *J Am Dent Assoc* 1989; 118(3):317–318.
10. Leao JC, Ferreira AM, Martins S, et al. Cheilitis glandularis: an unusual presentation in a patient with HIV infection. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 95(2):142–144.
11. Stoopler ET, Carrasco L, Stanton DC, et al. Cheilitis glandularis: an unusual histopathologic presentation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 95(3):312–317.
12. Lederman DA. Suppurative stomatitis glandularis. *Oral Surg Oral Med Oral Pathol* 1994; 78(3):319–322.
13. Musa NJ, Suresh L, Hatton M, et al. Multiple suppurative cystic lesions of the lips and buccal mucosa: a case of suppurative stomatitis glandularis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99(2):175–179.
4. Sneige N, Batsakis JG. Necrotizing sialometaplasia. *Ann Otol Rhinol Laryngol* 1992; 101(3):282–284.
5. Sandmeier D, Bouzourene H. Necrotizing sialometaplasia: a potential diagnostic pitfall. *Histopathology* 2002; 40(2): 200–201.
6. Rizkalla H, Toner M. Necrotizing sialometaplasia versus invasive carcinoma of the head and neck: the use of myoepithelial markers and keratin subtypes as an adjunct to diagnosis. *Histopathology* 2007; 51(2):184–189.
7. Anneroth G, Hansen LS. Necrotizing sialometaplasia. The relationship of its pathogenesis to its clinical characteristics. *Int J Oral Surg* 1982; 11(5):283–291.
8. Shigematsu H, Shigematsu Y, Noguchi Y, et al. Experimental study on necrotizing sialometaplasia of the palate in rats. Role of local anesthetic injections. *Int J Oral Maxillofac Surg* 1996; 2(3):239–241.
9. Rye LA, Calhoun NR, Redman RS. Necrotizing sialometaplasia in a patient with Buerger's disease and Raynaud's phenomenon. *Oral Surg Oral Med Oral Pathol* 1980; 49(3): 233–236.
10. Batsakis JG, Manning JT. Necrotizing sialometaplasia of major salivary glands. *J Laryngol Otol* 1987; 101(9): 962–966.
11. Hurt MA, Diaz-Arias AA, Rosenholtz MJ, et al. Posttraumatic lobular squamous metaplasia of breast. An unusual pseudocarcinomatous metaplasia resembling squamous (necrotizing) sialometaplasia of the salivary gland. *Mod Pathol* 1988; 1(5):385–390.
12. King DT, Barr RJ. Syringometaplasia: mucinous and squamous variants. *J Cutan Pathol* 1979; 6(4):284–291.
13. Zschoch H. (Mucus gland infarct with squamous epithelial metaplasia in the lung. A rare site of so-called necrotizing sialometaplasia). *Pathologie* 1992; 13(1):45–48.
14. Imbery TA, Edwards PA. Necrotizing sialometaplasia: literature review and case reports. *J Am Dent Assoc* 1996; 127(7):1087–1092.
15. Werning JT, Waterhouse JP, Mooney JW. Subacute necrotizing sialadenitis. *Oral Surg Oral Med Oral Pathol* 1990; 70(6):756–759.
16. Lombardi T, Samson J, Küffer R. Subacute necrotizing sialadenitis: a form of necrotizing sialometaplasia? *Arch Otolaryngol Head Neck Surg* 2003; 129(9):972–975.
17. Fowler CB, Brannon RB. Subacute necrotizing sialadenitis: report of 7 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 89(5): 600–609.
18. Suresh L, Aguirre A. Subacute necrotizing sialadenitis: a clinicopathological study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(3):385–390.

Necrotizing Sialometaplasia

1. Abrams AM, Melrose RJ, Howell FV. Necrotizing sialometaplasia. A disease simulating malignancy. *Cancer* 1973; 32 (1):130–135.
2. Mesa ML, Gertler RS, Schneider LC. Necrotizing sialometaplasia: frequency of histologic misdiagnosis. *Oral Surg Oral Med Oral Pathol* 1984; 57(1):71–73.
3. Brannon RB, Fowler CB, Hartman KS. Necrotizing sialometaplasia. A clinicopathologic study of sixty-nine cases and review of the literature. *Oral Surg Oral Med Oral Pathol* 1991; 72(3):317–325.

Subacute Necrotizing Sialadenitis

1. Werning JT, Waterhouse JP, Mooney JW. Subacute necrotizing sialadenitis. *Oral Surg Oral Med Oral Pathol* 1990; 70(6):756–759.
2. Van der Wal JE, Kraaijenhagen HA, van der Waal I. Subacute necrotizing sialadenitis: a new entity? *Br J Oral Maxillofac Surg* 1995; 33(5):302–303.
3. Fowler CB, Brannon RB. Subacute necrotizing sialadenitis: report of 7 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 89(5): 600–609.
4. Castro WH, Drummond SN, Gomez RS. Subacute necrotizing sialadenitis in the buccal mucosa. *J Oral Maxillofac Surg* 2002; 60(12):1494–1496.
5. Lombardi T, Samson J, Küffer R. Subacute necrotizing sialadenitis: a form of necrotizing sialometaplasia? *Arch Otolaryngol Head Neck Surg* 2003; 129(9):972–975.

- Suresh L, Aguirre A. Subacute necrotizing sialadenitis: a clinicopathological study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(3):385–390.

Recurrent Parotitis

- Ericson S, Zetterlund B, Ohman J. Recurrent parotitis and sialectasis in childhood. Clinical, radiologic, immunologic, bacteriologic, and histologic study. *Ann Otol Rhinol Laryngol* 1991; 100(7):527–535.
- Chitre VV, Premchandra DJ. Recurrent parotitis. *Arch Dis Child* 1997; 77(4):359–363.
- Sitheequ M, Sivachandran Y, Varathan V, et al. Juvenile recurrent parotitis: clinical, sialographic and ultrasonographic features. *Int J Paediatr Dent* 2007; 17(2):98–104.
- Konno A, Ito E. A study on the pathogenesis of recurrent parotitis in childhood. *Ann Otol Rhinol Laryngol Suppl* 1979; 88(6 pt 4 suppl 63):1–20.
- Nahlieli O, Shacham R, Shlesinger M, et al. Juvenile recurrent parotitis: a new method of diagnosis and treatment. *Pediatrics* 2004; 114(1):9–12.
- Patey DH, Thackray AC. Chronic “sialectatic” parotitis in the light of pathological studies on parotidectomy material. *Br J Surg* 1955; 43(177):43–50.
- Gnepp DR. Sclerosing polycystic adenosis of the salivary gland: a lesion that may be associated with dysplasia and carcinoma in situ. *Adv Anat Pathol* 2003; 10(4):218–222.
- Noonan VL, Kalmar JR, Allen CM, et al. Sclerosing polycystic adenosis of minor salivary glands: report of three cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(4):516–520.
- Skálová A, Michal M, Simpson RH, et al. Sclerosing polycystic adenosis of parotid gland with dysplasia and ductal carcinoma in situ. Report of three cases with immunohistochemical and ultrastructural examination. *Virchows Arch* 2002; 440(1):29–35.
- Bharadwaj G, Nawroz I, O'Regan B. Sclerosing polycystic adenosis of the parotid gland. *Br J Oral Maxillofac Surg* 2007; 45(1):74–76.
- Gnepp DR, Wang LJ, Brandwein-Gensler M, et al. Sclerosing polycystic adenosis of the salivary gland: a report of 16 cases. *Am J Surg Pathol* 2006; 30(2):154–164.
- Imamura Y, Morishita T, Kawakami M, et al. Sclerosing polycystic adenosis of the left parotid gland: report of a case with fine needle aspiration cytology. *Acta Cytol* 2004; 48(4):569–573.
- Kloppenborg RP, Sepmeijer JW, Sie-Go DM, et al. Sclerosing polycystic adenosis: a case report. *B-ENT* 2006; 2(4):189–192.
- Skálová A, Gnepp DR, Simpson RH, et al. Clonal nature of sclerosing polycystic adenosis of salivary glands demonstrated by using the polymorphism of the human androgen receptor (HUMARA) locus as a marker. *Am J Surg Pathol* 2006; 30(8):939–944.

Viral Sialadenitis Including Mumps, Cytomegalovirus, and HIV-Associated Lymphoepithelial Cyst

- McQuone SJ. Acute viral and bacterial infections of the salivary glands. *Otolaryngol Clin North Am* 1999; 32(5):793–811.
- Hviid A, Rubin S, Mühlemann K. Mumps. *Lancet* 2008; 371(9616):932–944.
- Werning JT. Infectious and systemic diseases. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:39–59.
- Schiodt M. HIV-associated salivary gland disease: a review. *Oral Surg Oral Med Oral Pathol* 1992; 73(2):164–167.
- Labouyrie E, Merlio JP, Beylot-Barry M, et al. Human immunodeficiency virus type 1 replication within cystic lymphoepithelial lesion of the salivary gland. *Am J Clin Pathol* 1993; 100(1):41–46.
- Ihrler S, Zietz C, Riederer A, et al. HIV-related parotid lymphoepithelial cysts. Immunohistochemistry and 3-D reconstruction of surgical and autopsy material with special reference to formal pathogenesis. *Virchows Arch* 1996; 429(2–3):139–147.
- Maiorano E, Favia G, Viale G. Lymphoepithelial cysts of salivary glands: an immunohistochemical study of HIV-related and HIV-unrelated lesions. *Hum Pathol* 1998; 29(3):260–265.
- Chetty R. HIV-associated lymphoepithelial cysts and lesions: morphological and immunohistochemical study of the lymphoid cells. *Histopathology* 1998; 33(3):222–229.
- Mandel L, Hong J. HIV-associated parotid lymphoepithelial cysts. *J Am Dent Assoc* 1999; 130(4):528–532.
- Dave SP, Pernas FG, Roy S. The benign lymphoepithelial cyst and a classification system for lymphocytic parotid gland enlargement in the pediatric HIV population. *Laryngoscope* 2007; 117(1):106–113.

Tumor-Like Lesions

Sclerosing Polycystic Adenosis

Sialosis

- Seifert G. Tumour-like lesions of the salivary glands. The new WHO classification. *Pathol Res Pract* 1992; 188(7):836–846.
- Pape SA, MacLeod RI, McLean NR, et al. Sialadenosis of the salivary glands. *Br J Plast Surg* 1995; 48(6):419–422.
- Kelly SA, Black MJ, Soames JV. Unilateral enlargement of the parotid gland in a patient with sialosis and contralateral parotid aplasia. *Br J Oral Maxillofac Surg* 1990; 28(6):409–412.
- Scully C, Bagán JV, Eveson JW, et al. Sialosis: 35 cases of persistent parotid swelling from two countries. *Br J Oral Maxillofac Surg* 2008; 46(6):468–472.
- Mignogna MD, Fedele S, Lo Russo L. Anorexia/bulimia-related sialadenosis of palatal minor salivary glands. *J Oral Pathol Med* 2004; 33(7):441–442.
- Seifert G, Miehleke A, Haubrich J, et al. Diseases of the Salivary Glands. Pathology—Diagnosis—Treatment—Facial Nerve Surgery. Stuttgart: Georg Thieme Verlag, 1986:78–84.
- Brick IB. Parotid enlargement in cirrhosis of the liver. *Ann Intern Med* 1958; 49(2):438–451.
- Buchner A, Sreebny LM. Enlargement of salivary glands. Review of the literature. *Oral Surg Oral Med Oral Pathol* 1972; 34(2):209–222.
- Donath K, Spillner M, Seifert G. The influence of the autonomic nervous system on the ultrastructure of the parotid acinar cells. Experimental contribution to the neurohormonal sialadenosis. *Virchows Arch A Pathol Anat Histol* 1974; 364(1):15–33.
- Mandic R, Teymoortash A, Kann PH, et al. Sialadenosis of the major salivary glands in a patient with central diabetes insipidus—implications of aquaporin water channels in the pathomechanism of sialadenosis. *Exp Clin Endocrinol Diabetes* 2005; 113(4):205–207.
- Davidson D, Leibel BS, Berris B. Asymptomatic parotid gland enlargement in diabetes mellitus. *Ann Intern Med* 1969; 70(1):31–38.

- Smith BC, Ellis GL, Slater LJ, et al. Sclerosing polycystic adenosis of major salivary glands. A clinicopathologic analysis of nine cases. *Am J Surg Pathol* 1996; 20(2):161–170.

12. Duggan JJ, Rothbell EN. Asymptomatic enlargement of the parotid glands. *N Engl J Med* 1957; 257(26):1262-1267.
13. Mandel L, Baumash H. Parotid enlargement due to alcoholism. *J Am Dent Assoc* 1971; 82(2):369-373.
14. Rothbell EN, Duggan JJ. Enlargement of the parotid gland in disease of the liver. *Am J Med* 1957; 22(3):367-372.
15. Vavrina J, Müller W, Gebbers JO. Enlargement of salivary glands in bulimia. *J Laryngol Otol* 1994; 108(6):516-518.
16. Coleman H, Altini M, Nayler S, et al. Sialadenosis: a presenting sign in bulimia. *Head Neck* 1998; 20(8):758-762.
17. Scully C, Eveson J. Sialosis and necrotising sialometaplasia in bulimia; a case report. *Int J Oral Maxillofac Surg* 2004; 33(8):808-810.
18. Kim D, Uy C, Mandel L. Sialosis of unknown origin. *N Y State Dent J* 1998; 64(7):38-40.
19. Donath K, Seifert G. Ultrastructural studies of the parotid glands in sialadenosis. *Virchows Arch A Pathol Anat Histol* 1975; 365(2):119-135.
20. Thackray AC, Lucas RB. Sialosis. In: *Atlas of Tumor Pathology: Tumors of the Major Salivary Glands*, 2nd series, fascicle 10. Washington DC: Armed Forces Institute of Pathology, 1974:133-134.
21. Batsakis JG. Pathology consultation. Sialadenosis. *Ann Otol Rhinol Laryngol* 1988; 97(1):94-95.
22. Ellis GL, Auclair PL. Sialadenosis. In: *Tumors of the Salivary Glands. Atlas of Tumor Pathology*, 3rd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:434-435.
5. Morgan WS, Castleman BA. A clinicopathologic study of "Mikulicz's disease". *Am J Pathol* 1953; 29:471-489.
6. Yamamoto M, Takahashi H, Ohara M, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006; 16(6):335-340.
7. Ellis GL, Auclair PL. Benign lymphoepithelial lesion. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:411-413.
8. Godwin JT. Benign lymphoepithelial lesion of the parotid gland adenolymphoma, chronic inflammation, lymphoepithelioma, lymphocytic tumor, Mikulicz disease. *Cancer* 1952; 5:1089-1103.
9. Bridges AJ, England DM. Benign lymphoepithelial lesion: relationship to Sjögren's syndrome and evolving malignant lymphoma. *Semin Arthritis Rheum* 1989; 19(3):201-208.
10. Falzon M, Isaacson PG. The natural history of benign lymphoepithelial lesion of the salivary gland in which there is a monoclonal population of B cells. A report of two cases. *Am J Surg Pathol* 1991; 15(1):59-65.
11. Palmer RM, Eveson JW, Gusterson BA. "Epimyoeplithelial" islands in lymphoepithelial lesions: an immunocytochemical study. *Virchows Arch [Pathol Anat]* 1986; 408(6):603-609.
12. Ihrler S, Zietz C, Sendelhofert A, et al. Lymphoepithelial duct lesions in Sjögren-type sialadenitis. *Virchows Arch* 1999; 434(4):315-323.
13. Bowman SJ, Ibrahim GH, Holmes G, et al. Estimating the prevalence among Caucasian women of primary Sjögren's syndrome in two general practices in Birmingham, UK. *Scand J Rheumatol* 2004; 33(1):39-43.
14. Scott CA, Avellini C, Desinan L, et al. Chronic lymphocytic sialadenitis in HCV-related chronic liver disease: comparison with Sjögren's syndrome. *Histopathology* 1997; 30(1):41-48.
15. Jaffe ES. Lymphoid lesions of the head and neck: a model of lymphocyte homing and lymphomagenesis. *Mod Pathol* 2002; 15(3):255-263.
16. Fox RI. Sjögren's syndrome. *Lancet* 2005; 366(9482):321-331.
17. Delaleu N, Jonsson R, Koller MM. Sjögren's syndrome. *Eur J Oral Sci* 2005; 113(2):101-113.
18. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61(6):554-558.
19. Quintana PG, Kapadia SB, Bahler DW, et al. Salivary gland lymphoid infiltrates associated with lymphoepithelial lesions: a clinicopathologic, immunophenotypic, and genotypic study. *Hum Pathol* 1997; 28(7):850-861.
20. Bahler DW, Swerdlow SH. Clonal salivary gland infiltrates associated with myoepithelial sialadenitis (Sjögren's syndrome) begin as non-malignant antigen-associated expansions. *Blood* 1998; 91(6):1864-1872.
21. Mahlstedt K, Ussmuller J, Donath K. Value of minor salivary gland biopsy in diagnosing Sjögren's syndrome. *J Otolaryngol* 2002; 31(5):299-303.
22. Harris NL, Isaacson PG. What are the criteria for distinguishing MALT from non-MALT lymphoma at extranodal sites? *Am J Clin Pathol* 1999; 111(suppl 1):S126-S132.
23. Nagao T, Ishida Y, Sugano I, et al. Epstein-Barr virus-associated undifferentiated carcinoma with lymphoid stroma of the salivary gland in Japanese patients: comparison with benign lymphoepithelial lesion. *Cancer* 1996; 78(4):695-703.
24. Ma J, Chan JK, Chow CW, et al. Lymphadenoma: a report of three cases of an uncommon salivary gland neoplasm. *Histopathology* 2002; 41(4):342-350.
25. Daniels TE. Benign lymphoepithelial lesion and Sjögren's syndrome. In Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical*

Salivary Gland Hyperplasia

1. Yu GY, Donath K. Adenomatous ductal proliferation of the salivary gland. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 91(2):215-221.
2. Luna MA. Salivary gland hyperplasia. *Adv Anat Pathol* 2002; 9(4):251-255.
3. Arafat A, Brannon RB, Ellis GL. Adenomatoid hyperplasia of mucous salivary glands. *Oral Surg Oral Med Oral Pathol* 1981; 52(1):51-55.
4. Nozaki S, Araki A, Nakagawa K, et al. Adenomatoid hyperplasia of the palate in an Asian child. *J Oral Maxillofac Surg* 1996; 54(5):627-678.
5. Campos LA. Hyperplasia of the sublingual glands in adult patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 81(5):584-585.
6. Domaneschi C, Mauricio AR, Modolo F, et al. Idiopathic hyperplasia of the sublingual glands in totally or partially edentulous individuals. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(3):374-377.
7. Chetty R. Intercalated duct hyperplasia: possible relationship to epithelial-myoepithelial carcinoma and hybrid tumours of salivary gland. *Histopathology* 2000; 37(3):260-263.

Lymphoepithelial Sialadenitis and Sjögren's Syndrome

1. Harris NL. Lymphoid proliferations of the salivary glands. *Am J Clin Pathol* 1999; 111(suppl 1):S94-S103.
2. Mikulicz J. Über eine eigenartige symmetrische Erkrankung der Tränen- und Mundspeicheldrüsen. *Beitr Z Chir Festschr Theodor Billroth* 1892; 2:610-630.
3. Schaffer AJ, Jacobsen AW. Mikulicz's disease: a report of ten cases. *Am J Dis Child* 1927; 34:327-346.
4. Sjögren H. Zur Kenntnis der Keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Trännendrüsen). *Acta Ophthalmol (suppl)* 1933; 2:1-151.

Pathology of the Salivary Glands. Philadelphia: W B Saunders Co, 1991:83–106.

26. Chetty R. HIV-associated lymphoepithelial cysts and lesions: morphological and immunohistochemical study of the lymphoid cells. *Histopathology* 1998; 33(3): 222–229.
- ## Introduction to Salivary Gland Tumors
1. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg* 1999; 120(6):834–840.
 2. Evans RW, Cruikshank AH. *Epithelial Tumours of the Salivary Glands*. Philadelphia: WB Saunders, 1970:9–10.
 3. Lennox B, Clarke JA, Drake F, et al. Incidence of salivary gland tumours in Scotland: accuracy of national records. *Br Med J* 1978; 1(6114):687–689.
 4. Gunn A, Parrott NR. Parotid tumours: a review of parotid tumour surgery in the Northern Regional Health Authority of the United Kingdom 1978–1982. *Br J Surg* 1988; 75(11): 1144–1146.
 5. Auclair PL, Ellis GL, Gnepp DR, et al. Salivary gland neoplasms: general considerations. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:135–164.
 6. Sun EC, Curtis R, Melbye M, et al. Salivary gland cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 1999; 8(12):1095–1100.
 7. Ostman J, Anneroth G, Gustafsson H, et al. Malignant salivary gland tumours in Sweden 1960–1989—an epidemiological study. *Oral Oncol* 1997; 33(3):169–176.
 8. Koivunen P, Suutala L, Schorsch I, et al. Malignant epithelial salivary gland tumors in northern Finland: incidence and clinical characteristics. *Eur Arch Otorhinolaryngol* 2002; 259(3):146–149.
 9. Rees LAG, Hankey BF, Miller BA, et al. *Cancer statistics review 1973–88*. Bethesda, MD: National Cancer Institute, 1991 (NIH publication no. 91–2789).
 10. Horn-Ross PL, West DW, Brown SR. Recent trends in the incidence of salivary gland cancer. *Int J Epidemiol* 1991; 20(3):628–633.
 11. Rippin JW, Potts AJ. Intra-oral salivary gland tumours in the West Midlands. *Br Dent J* 1992; 173(1):17–19.
 12. Zheng T, Holford TR, Chen Y, et al. Are cancers of the salivary gland increasing? Experience from Connecticut, USA. *Int J Epidemiol* 1997; 26(2):264–271.
 13. Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. *Otolaryngol Head Neck Surg* 2006; 135(3):451–457.
 14. Carvalho AL, Nishimoto IN, Califano JA, et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer* 2005; 114(5):806–816.
 15. Dorn HF, Cutler SJ. Morbidity from cancer in the United States. In: *Public Health Monograph No 56*. Washington DC. U.S. Government Printing Office, 1959,186.
 16. Schaefer O, Hildes JA, Medd LM, et al. The changing pattern of neoplastic disease in Canadian Eskimos. *Can Med Assoc J* 1975; 112(12):1399–1404.
 17. Hildes JA, Schaefer O. The changing picture of neoplastic disease in the western and central Canadian Arctic (1950–1980). *Can Med Assoc J* 1984; 130(1):25–32.
 18. Loke YW. Salivary gland tumours in Malaya. *Br J Cancer* 1967; 21(4):665–674.
 19. Wang D, Li Y, He H, et al. Intraoral minor salivary gland tumors in a Chinese population: a retrospective study on 737 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(1):94–100.
 20. Eveson JW, Auclair P, Gnepp DR, et al. Tumours of the salivary gland: introduction. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:212–215.
 21. Eneroth CM. Salivary gland tumors in the parotid gland, submandibular gland, and the palate region. *Cancer* 1971; 27(6):1415–1418.
 22. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol* 1985; 146(1):51–58.
 23. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg* 1986; 8(3):177–184.
 24. Seifert G, Miehke A, Haubrich J, et al. *Diseases of the Salivary Glands. Pathology – Diagnosis – Treatment – Facial Nerve Surgery*. Stuttgart: Georg Thieme Verlag, 1986.
 25. Pires FR, Pringle GA, de Almeida OP, et al. Intra-oral minor salivary gland tumors: a clinicopathological study of 546 cases. *Oral Oncol* 2007; 43(5):463–470.
 26. Pires FR, de Almeida OP, Pringle G, et al. Differences on clinicopathological profile from intraoral minor salivary gland tumors around the world. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 105(2):136–138.
 27. Saw D, Lau WH, Ho JH, et al. Malignant lymphoepithelial lesion of the salivary gland. *Hum Pathol* 1986; 17(9): 914–923.
 28. Tsai CC, Chen CL, Hsu HC. Expression of Epstein-Barr virus in carcinomas of major salivary glands: a strong association with lymphoepithelioma-like carcinoma. *Hum Pathol* 1996; 27(3):258–262.
 29. Wang CP, Chang YL, Ko JY, et al. Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands. *Cancer* 2004; 101(9):2020–2027.
 30. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. *Am J Clin Pathol* 1995; 103(3):308–315.
 31. Hamilton-Dutoit SJ, Therkildsen MH, Neilsen NH, et al. Undifferentiated carcinoma of the salivary gland in Greenlandic Eskimos: demonstration of Epstein-Barr virus DNA by in situ nucleic acid hybridization. *Hum Pathol* 1991; 22(8):811–815.
 32. Manganaris A, Patakiouta F, Xirou P, et al. Lymphoepithelial carcinoma of the parotid gland: is an association with Epstein-Barr virus possible in non-endemic areas? *Int J Oral Maxillofac Surg* 2007; 36(6):556–559.
 33. Laane CJ, Murr AH, Mhatre AN, et al. Role of Epstein-Barr virus and cytomegalovirus in the etiology of benign parotid tumors. *Head Neck* 2002; 24(5):443–450.
 34. Malinvaud D, Couloigner V, Badoual C, et al. Pleomorphic adenoma of the nasal septum and its relationship with Epstein-Barr virus. *Auris Nasus Larynx* 2006; 33(4):417–421.
 35. Martinelli M, Martini F, Rinaldi E, et al. Simian virus 40 sequences and expression of the viral large T antigen oncoprotein in human pleomorphic adenomas of parotid glands. *Am J Pathol* 2002; 161(4):1127–1133.
 36. Belsky JL, Tachikawa K, Cihak RW, et al. Salivary gland tumors in atomic bomb survivors, Hiroshima-Nagasaki, 1957 to 1970. *JAMA* 1972; 219(7):864–868.
 37. Belsky JL, Takeichi N, Yamamoto T, et al. Salivary gland neoplasms following atomic radiation: additional cases and reanalysis of combined data in a fixed population, 1957–1970. *Cancer* 1975; 35(2):555–559.
 38. Takeichi N, Hirose F, Yamamoto H. Salivary gland tumors in atomic bomb survivors, Hiroshima, Japan. I. Epidemiologic observations. *Cancer* 1976; 38(6):2462–2468.
 39. Takeichi N, Hirose F, Yamamoto H, et al. Salivary gland tumors in atomic bomb survivors, Hiroshima, Japan. II.

- Pathologic study and supplementary epidemiologic observations. *Cancer* 1983; 52(2):377-385.
40. Saku T, Hayashi Y, Takahara O, et al. Salivary gland tumors among atomic bomb survivors, 1950-1987. *Cancer* 1997; 79(8):1465-1475.
 41. Schneider AB, Favus MJ, Stachura ME, et al. Salivary gland neoplasms as a late consequence of head and neck irradiation. *Ann Intern Med* 1977; 87(2):160-164.
 42. Ron E, Saftlas AF. Head and neck radiation carcinogenesis: epidemiologic evidence. *Otolaryngol Head Neck Surg* 1996; 115(5):403-408.
 43. Modan B, Chetrit A, Alfandary E, et al. Increased risk of salivary gland tumors after low-dose irradiation. *Laryngoscope* 1998; 108(7):1095-1097.
 44. Mihailescu D, Shore-Freedman E, Mukani S, et al. Multiple neoplasms in an irradiated cohort: pattern of occurrence and relationship to thyroid cancer outcome. *J Clin Endocrinol Metab* 2002; 87(7):3236-3241.
 45. Hoffman DA, McConahey WM, Fraumeni JF Jr., et al. Cancer incidence following treatment of hyperthyroidism. *Int J Epidemiol* 1982; 11(3):218-224.
 46. Preston-Martin S, Thomas DC, White SC, et al. Prior exposure to medical and dental x-rays related to tumors of the parotid gland. *J Natl Cancer Inst* 1988; 80(12):943-949.
 47. Preston-Martin S, White SC. Brain and salivary gland tumors related to prior dental radiography: implications for current practice. *J Am Dent Assoc* 1990; 120(2):151-158.
 48. Spitz MR, Sider JG, Newell GR, et al. Incidence of salivary gland cancer in the United States relative to ultraviolet radiation exposure. *Head Neck Surg* 1988; 10(5):305-308.
 49. Spitz MR, Sider JG, Newell GR. Salivary gland cancer and risk of subsequent skin cancer. *Head Neck* 1990; 12(3):254-256.
 50. Whatley WS, Thompson JW, Rao B. Salivary gland tumors in survivors of childhood cancer. *Otolaryngol Head Neck Surg* 2006; 134(3):385-388.
 51. Lönn S, Ahlbom A, Christensen HC, et al. Mobile phone use and risk of parotid gland tumor. *Am J Epidemiol* 2006; 164(7):637-643.
 52. Schüz J, Jacobsen R, Olsen JH, et al. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. *J Natl Cancer Inst* 2006; 98(23):1707-1713.
 53. Sadetzki S, Chetrit A, Jarus-Hakak A, et al. Cellular phone use and risk of benign and malignant parotid gland tumors—a nationwide case-control study. *Am J Epidemiol* 2008; 167(4):457-467.
 54. Miller AS, Harwick RD, Alfaro-Miranda M, et al. Search for correlation of radon levels and incidence of salivary gland tumors. *Oral Surg Oral Med Oral Pathol* 1993; 75(1):58-63.
 55. Mancuso TF, Brennan MJ. Epidemiological considerations of cancer of the gallbladder, bile ducts and salivary glands in the rubber industry. *J Occup Med* 1970; 12(9):333-341.
 56. Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. *Epidemiology* 1997; 8(4):414-419.
 57. Milham S Jr. Cancer mortality pattern associated with exposure to metals. *Ann N Y Acad Sci* 1976; 271:243-249.
 58. Swanson GM, Belle SH. Cancer morbidity among woodworkers in the US automotive industry. *J Occup Med* 1982; 24(4):315-319.
 59. Wilson RT, Moore LE, Dosemeci M. Occupational exposures and salivary gland cancer mortality among African American and white workers in the United States. *J Occup Environ Med* 2004; 46(3):287-297.
 60. Swanson GM, Burns PB. Cancer incidence among women in the workplace: a study of the association between occupation and industry and 11 cancer sites. *J Occup Environ Med* 1995; 37(3):282-287.
 61. Swanson GM, Burns PB. Cancers of the salivary gland: workplace risks among women and men. *Ann Epidemiol* 1997; 7(6):369-374.
 62. Takkouche B, Etminan M, Montes-Martínez A. Personal use of hair dyes and risk of cancer: a meta-analysis. *JAMA* 2005; 293(20):2516-2525.
 63. Graham S, Blanchet M, Rohrer T. Cancer in asbestos-mining and other areas of Quebec. *J Natl Cancer Inst* 1977; 59(4):1139-1145.
 64. Muscat JE, Wynder EL. A case/control study of risk factors for major salivary gland cancer. *Otolaryngol Head Neck Surg* 1998; 118(2):195-198.
 65. Keller AZ. Residence, age, race and related factors in the survival and associations with salivary tumors. *Am J Epidemiol* 1969; 90(4):269-277.
 66. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* 1977; 5(3):525-547.
 67. Horn-Ross PL, Morrow M, Ljung BM. Diet and the risk of salivary gland cancer. *Am J Epidemiol* 1997; 146(2):171-176.
 68. Zheng W, Shu XO, Ji BT, et al. Diet and other risk factors for cancer of the salivary glands: a population-based case-control study. *Int J Cancer* 1996; 67(2):194-198.
 69. Dietz A, Barme B, Gewelke U, et al. The epidemiology of parotid tumors. A case control study. *HNO* 1993; 41(2):83-90.
 70. Suba Z, Barabás J, Szabó G, et al. Increased prevalence of diabetes and obesity in patients with salivary gland tumors. *Diabetes Care* 2005; 28(1):228.
 71. Dimery IW, Jones LA, Verjan RP, et al. Estrogen receptors in normal salivary gland and salivary gland carcinoma. *Arch Otolaryngol Head Neck Surg* 1987; 113(10):1082-1085.
 72. Dori S, Trougouboff P, David R, et al. Immunohistochemical evaluation of estrogen and progesterone receptors in adenoid cystic carcinoma of salivary gland origin. *Oral Oncol* 2000; 36(5):450-453.
 73. Jeannon JP, Soames JV, Bell H, et al. Immunohistochemical detection of oestrogen and progesterone receptors in salivary tumours. *Clin Otolaryngol* 1999; 24(1):52-54.
 74. Shick PC, Riordan GP, Foss RD. Estrogen and progesterone receptors in salivary gland adenoid cystic carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 80(4):440-444.
 75. Miller AS, Hartman GG, Chen SY, et al. Estrogen receptor assay in polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma of salivary gland origin. An immunohistochemical study. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):36-40.
 76. Pires FR, da Cruz Perez DE, de Almeida OP, et al. Estrogen receptor expression in salivary gland mucoepidermoid carcinoma and adenoid cystic carcinoma. *Pathol Oncol Res* 2004; 10(3):166-168.
 77. Molteni A, Warpeha RL, Brizio-Molteni L, et al. Estradiol receptor-binding protein in head and neck neoplastic and normal tissue. *Arch Surg* 1981; 116(2):207-210.
 78. Onitsuka T. Sex hormones in papillary carcinoma of thyroid gland and pleomorphic adenoma of parotid gland. *Acta Otolaryngol* 1994; 114(12):218-222.
 79. Nasser SM, Faquin WC, Dayal Y. Expression of androgen, estrogen, and progesterone receptors in salivary gland tumors. Frequent expression of androgen receptor in a subset of malignant salivary gland tumors. *Am J Clin Pathol* 2003; 119(6):801-806.
 80. Williams MD, Roberts D, Blumenschein GR Jr., et al. Differential expression of hormonal and growth factor receptors in salivary duct carcinomas: biologic significance

and potential role in therapeutic stratification of patients. *Am J Surg Pathol* 2007; 31(11):1645–1652.

81. Glas AS, Hollema H, Nap RE, et al. Expression of estrogen receptor, progesterone receptor, and insulin-like growth factor receptor-1 and of Ki-67 in patients with recurrent pleomorphic adenoma of the parotid gland. *Cancer* 2002; 94(8):2211–2216.
82. Barnes L, Rao U, Contis L, et al. Salivary duct carcinoma. Part II. Immunohistochemical evaluation of 13 cases for estrogen and progesterone receptors, cathepsin D, and c-erbB-2 protein. *Oral Surg Oral Med Oral Pathol* 1994; 78(1):74–80.
83. Ozono S, Onozuka M, Sato K, et al. Immunohistochemical localization of estradiol, progesterone, and progesterone receptor in human salivary glands and salivary adenoid cystic carcinomas. *Cell Struct Funct* 1992; 17(3):169–175.
84. Kapadia SB, Barnes L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. *Mod Pathol* 1998; 11(11):1033–1038.
85. Fan CY, Wang J, Barnes EL. Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma: an immunohistochemical analysis of 13 cases and review of the literature. *Am J Surg Pathol* 2000; 24(4):579–586.
86. Fan CY, Melhem MF, Hosal AS, et al. Expression of androgen receptor, epidermal growth factor receptor, and transforming growth factor alpha in salivary duct carcinoma. *Arch Otolaryngol Head Neck Surg* 2001; 127(9):1075–1079.

Imaging

1. Yousem DM, Kraut MA, Chalian AA. Major salivary gland imaging. *Radiology* 2000; 216(1):19–29.
2. Howlett DC, Kesse KW, Hughes DV, et al. The role of imaging in the evaluation of parotid disease. *Clin Radiol* 2002; 57(5):692–701.
3. Howlett DC. High resolution ultrasound assessment of the parotid gland. *Br J Radiol* 2003; 76(904):271–277.
4. Gritzmann N, Rettenbacher T, Hollerweger A, et al. Sonography of the salivary glands. *Eur Radiol* 2003; 13(5):964–975.
5. Shah GV. MR imaging of salivary glands. *Neuroimaging Clin N Am* 2004; 14(4):777–808.
6. Madani G, Beale T. Tumors of the salivary glands. *Semin Ultrasound CT MR* 2006; 27(6):452–464.
7. Bialek EJ, Jakubowski W, Zajkowski P, et al. US of the major salivary glands: anatomy and spatial relationships, pathologic conditions, and pitfalls. *Radiographics* 2006; 26(3):745–763.
8. Lee YY, Wong KT, King AD, et al. Imaging of salivary gland tumours. *Eur J Radiol* 2008; 66(3):419–436.
9. Yabuuchi H, Fukuya T, Tajima T, et al. Salivary gland tumors: diagnostic value of gadolinium-enhanced dynamic MR imaging with histopathologic correlation. *Radiology* 2003; 226(2):345–354.
10. Ishikawa H, Ishii Y. Evaluation of salivary gland tumors with ^{99m}Tc-pertechnetate. *J Oral Maxillofac Surg* 1984; 42(7):429–434.
11. Bradley MJ, Durham LH, Lancer JM. The role of colour flow Doppler in the investigation of the salivary gland tumour. *Clin Radiol* 2000; 55(10):759–762.
12. Madani G, Beale T. Inflammatory conditions of the salivary glands. *Semin Ultrasound CT MR* 2006; 27(6):440–451.
13. Ohbayashi N, Yamada I, Yoshino N, et al. Sjögren syndrome: comparison of assessments with MR sialography and conventional sialography. *Radiology* 1998; 209(3):683–688.
14. Niemelä RK, Pääkkö E, Suramo I, et al. Magnetic resonance imaging and magnetic resonance sialography of parotid glands in primary Sjögren's syndrome. *Arthritis Rheum* 2001; 45(6):512–518.

Fine-Needle Aspiration Cytology

1. Ellis GL, Auclair PL. Fine-needle aspiration biopsy of salivary glands. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:441–463.
2. Klijanienko J, Vielh P. Salivary Gland Tumors. Monographs in Clinical Cytology. Vol. 15. Basel, Switzerland: Karger, 2000.
3. Gnepp DR, Brandwein MS, Henley JD. Salivary and lacrimal glands. In: Gnepp DR, ed. *Surgical Pathology of the Head and Neck*. Philadelphia: WB Saunders, 2001.
4. Zbären P, Nuyens M, Loosli H, et al. Diagnostic accuracy of fine-needle aspiration cytology and frozen section in primary parotid carcinoma. *Cancer* 2004; 100(9):1876–1883.
5. Seethala RR, LiVolsi VA, Baloch ZW. Relative accuracy of fine-needle aspiration and frozen section in the diagnosis of lesions of the parotid gland. *Head Neck* 2005; 27(3):217–223.
6. Hughes JH, Volk EE, Wilbur DC. Cytopathology Resource Committee, College of American Pathologists. Pitfalls in salivary gland fine-needle aspiration cytology: lessons from the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. *Arch Pathol Lab Med* 2005; 129(1):26–31.
7. Stewart CJ, MacKenzie K, McGarry GW, et al. Fine-needle aspiration cytology of salivary gland: a review of 341 cases. *Diagn Cytopathol* 2000; 22(3):139–146.
8. Cohen EG, Patel SG, Lin O, et al. Fine-needle aspiration biopsy of salivary gland lesions in a selected patient population. *Arch Otolaryngol Head Neck Surg* 2004; 130(6):773–778.
9. Rajwanshi A, Gupta K, Gupta N, et al. Fine-needle aspiration cytology of salivary glands: diagnostic pitfalls—revisited. *Diagn Cytopathol* 2006; 34(8):580–584.
10. Schindler S, Nayar R, Dutra J, et al. Diagnostic challenges in aspiration cytology of the salivary glands. *Semin Diagn Pathol* 2001; 18(2):124–146.

Frozen Section diagnosis

1. Auclair PL, Ellis GL, Gnepp DR, et al. Salivary gland neoplasms: general considerations. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:135–164.
2. Gnepp DR, Brandwein MS, Henley JD. Salivary and lacrimal glands. In: Gnepp DR, eds. *Surgical Pathology of the Head and Neck*. Philadelphia: WB Saunders, 2001.
3. Wong DS. Frozen section during parotid surgery revisited: efficacy of its applications and changing trend of indications. *Head Neck* 2002; 24(2):191–197.
4. Zbären P, Nuyens M, Loosli H, et al. Diagnostic accuracy of fine-needle aspiration cytology and frozen section in primary parotid carcinoma. *Cancer* 2004; 100(9):1876–1883.
5. Seethala RR, LiVolsi VA, Baloch ZW. Relative accuracy of fine-needle aspiration and frozen section in the diagnosis of lesions of the parotid gland. *Head Neck* 2005; 27(3):217–223.
6. Arabi Mianroodi AA, Sigston EA, Vallance NA. Frozen section for parotid surgery: should it become routine? *ANZ J Surg* 2006; 76(8):736–739.
7. Badoual C, Rousseau A, Heudes D, et al. Evaluation of frozen section diagnosis in 721 parotid gland lesions. *Histopathology* 2006; 49(5):538–540.

Genetics

1. Leivo I. Insights into a complex group of neoplastic disease: advances in histopathologic classification and molecular pathology of salivary gland cancer. *Acta Oncol* 2006; 45(6):662–668.

2. Cheuk W, Chan JK. Advances in salivary gland pathology. *Histopathology* 2007; 51(1):1–20.
3. Bullerdiek J, Wobst G, Meyer-Bolte K, et al. Cytogenetic subtyping of 220 salivary gland pleomorphic adenomas: correlation to occurrence, histological subtype, and in vitro cellular behavior. *Cancer Genet Cytogenet* 1993; 65(1): 27–31.
4. Eveson JW, Kusafuka K, Stenman G, et al. Pleomorphic adenoma. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:254–258.
5. Kas K, Voz ML, Röijer E, et al. Promoter swapping between the genes for a novel zinc finger protein and beta-catenin in pleiomorphic adenomas with t(3;8)(p21;q12) translocations. *Nat Genet* 1997; 15(2):170–174.
6. Voz ML, Aström AK, Kas K, et al. The recurrent translocation t(5;8)(p13;q12) in pleomorphic adenomas results in upregulation of PLAG1 gene expression under control of the LIFR promoter. *Oncogene* 1998; 16(11):1409–1416.
7. Aström AK, Voz ML, Kas K, et al. Conserved mechanism of PLAG1 activation in salivary gland tumors with and without chromosome 8q12 abnormalities: identification of SII as a new fusion partner gene. *Cancer Res* 1999; 59(4): 918–923.
8. Asp J, Persson F, Kost-Alimova M, et al. CHCHD7-PLAG1 and TCEA1-PLAG1 gene fusions resulting from cryptic, intrachromosomal 8q rearrangements in pleomorphic salivary gland adenomas. *Genes Chromosomes Cancer* 2006; 45(9):820–828.
9. Voz ML, Agten NS, Van de Ven WJ, et al. PLAG1, the main translocation target in pleomorphic adenoma of the salivary glands, is a positive regulator of IGF-II. *Cancer Res* 2000; 60(1):106–113.
10. Van Dyck F, Declercq J, Braem CV, et al. PLAG1, the prototype of the PLAG gene family: versatility in tumour development (review). *Int J Oncol* 2007; 30(4):765–774.
11. Geurts JM, Schoenmakers EF, Röijer E, et al. Expression of reciprocal hybrid transcripts of HMGIC and FHIT in a pleomorphic adenoma of the parotid gland. *Cancer Res* 1997; 57(1):13–17.
12. Geurts JM, Schoenmakers EF, Röijer E, et al. Identification of NFIB as recurrent translocation partner gene of HMGIC in pleomorphic adenomas. *Oncogene* 1998; 16(7): 865–872.
13. Queimado L, Lopes CS, Reis AM. WIF1, an inhibitor of the Wnt pathway, is rearranged in salivary gland tumors. *Genes Chromosomes Cancer* 2007; 46(3):215–225.
14. Röijer E, Nordkvist A, Ström AK, et al. Translocation, deletion/amplification, and expression of HMGIC and MDM2 in a carcinoma ex pleomorphic adenoma. *Am J Pathol* 2002; 160(2):433–440.
15. Cleynen I, Van de Ven WJ. The HMGA proteins: a myriad of functions. *Int J Oncol* 2008; 32(2):289–305 (review).
16. Behboudi A, Enlund F, Winnes M, et al. Molecular classification of mucoepidermoid carcinomas-prognostic significance of the MECT1-MAML2 fusion oncogene. *Genes Chromosomes Cancer* 2006; 45(5):470–481.
17. Okabe M, Miyabe S, Nagatsuka H, et al. MECT1-MAML2 fusion transcript defines a favorable subset of mucoepidermoid carcinoma. *Clin Cancer Res* 2006; 12(13):3902–3907.
18. Tirado Y, Williams MD, Hanna EY, et al. CRTC1/MAML2 fusion transcript in high grade mucoepidermoid carcinomas of salivary and thyroid glands and Warthin's tumors: implications for histogenesis and biologic behavior. *Genes Chromosomes Cancer* 2007; 46(7):708–715.
19. Tonon G, Modi S, Wu L, et al. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. *Nat Genet* 2003; 33(2):208–213.
20. Möller E, Stenman G, Mandahl N, et al. POU5F1, encoding a key regulator of stem cell pluripotency, is fused to EWSR1 in hidradenoma of the skin and mucoepidermoid carcinoma of the salivary glands. *J Pathol* 2008; 215(1):78–86.
21. Yu Y, Baras AS, Shirasuna K, et al. Concurrent loss of heterozygosity and copy number analysis in adenoid cystic carcinoma by SNP genotyping arrays. *Lab Invest* 2007; 87(5): 430–439.
22. Stallmach I, Zenklusen P, Komminoth P, et al. Loss of heterozygosity at chromosome 6q23-25 correlates with clinical and histologic parameters in salivary gland adenoid cystic carcinoma. *Virchows Arch* 2002; 440(1):77–84.
23. El-Naggar AK, Abdul-Karim FW, Hurr K, et al. Genetic alterations in acinic cell carcinoma of the parotid gland determined by microsatellite analysis. *Cancer Genet Cytogenet* 1998; 102(1):19–24.
24. El-Naggar AK, Callender D, Coombes MM, et al. Molecular genetic alterations in carcinoma ex-pleomorphic adenoma: a putative progression model? *Genes Chromosomes Cancer* 2000; 27(2):162–168.
25. Choi HR, Batsakis JG, Callender DL, et al. Molecular analysis of chromosome 16q regions in dermal analogue tumors of salivary glands: a genetic link to dermal cylindroma? *Am J Surg Pathol* 2002; 26(6):778–783.
26. Skálová A, Stárek I, Vanecek T, et al. Expression of HER-2/*neu* gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence *in-situ* hybridization and immunohistochemistry. *Histopathology* 2003; 42(4): 348–356.
27. Glisson B, Colevas AD, Haddad R, et al. HER2 expression in salivary gland carcinoma: Dependence on histological subtype. *Clin Cancer Res* 2004; 10(3):944–946.
28. Cornolti G, Ungari M, Morassi ML, et al. Amplification and overexpression of HER2/*neu* gene and HER2/*neu* protein in salivary duct carcinoma of the parotid gland. *Arch Otolaryngol Head Neck Surg* 2007; 133(10):1031–1036.
29. Frierson HF Jr., El-Naggar AK, Welsh JB, et al. Large scale molecular analysis identifies genes with altered expression in salivary adenoid cystic carcinoma. *Am J Pathol* 2002; 161(4):1315–1323.
30. Leivo I, Jee KJ, Heikinheimo K, et al. Characterization of gene expression in major types of salivary gland carcinomas with epithelial differentiation. *Cancer Genet Cytogenet* 2005; 156(2):104–113.
31. Pastore A, Carinci F, Pelucchi S. Genetic expression profiling of parotid neoplasms by cDNA microarrays. *Acta Otorhinolaryngol Ital* 2005; 25(3):153–160.
32. Maruya S, Kurotaki H, Wada R, et al. Promoter methylation and protein expression of the E-cadherin gene in the clinicopathologic assessment of adenoid cystic carcinoma. *Mod Pathol* 2004; 17(6):637–645.
33. Zhang CY, Mao L, Li L, et al. Promoter methylation as a common mechanism for inactivating E-cadherin in human salivary gland adenoid cystic carcinoma. *Cancer* 2007; 110(1):87–95.
34. Li J, El-Naggar A, Mao L. Promoter methylation of p16INK4a, RASSF1A, and DAPK is frequent in salivary adenoid cystic carcinoma. *Cancer* 2005; 104(4):771–776.
35. Daa T, Kashima K, Kondo Y, et al. Aberrant methylation in promoter regions of cyclin-dependent kinase inhibitor genes in adenoid cystic carcinoma of the salivary gland. *APMIS* 2008; 116(2):21–26.
36. Guo XL, Sun SZ, Wang WX, et al. Alterations of p16INK4a tumour suppressor gene in mucoepidermoid carcinoma of the salivary glands. *Int J Oral Maxillofac Surg* 2007; 36(4): 350–353.
37. Williams MD, Chakravarti N, Kies MS, et al. Implications of methylation patterns of cancer genes in salivary gland tumors. *Clin Cancer Res* 2006; 12(24):7353–7358.

38. Kishi M, Nakamura M, Nishimine M, et al. Genetic and epigenetic alteration profiles for multiple genes in salivary gland carcinomas. *Oral Oncol* 2005; 41(2):161–169.

Classification

1. Ellis GL, Auclair PL. Classification of salivary gland neoplasms. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:129–134.
2. Eveson JW. WHO histological classification of tumours of the salivary glands. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:210.

Staging

1. Greene FL, Page DL, Fleming ID, et al. *American Joint Committee on Cancer. Cancer Staging Manual*. 6th ed. New York: Springer, 2002.
2. Sobin LH, Wittekind C. *TNM: Classification of Malignant Tumours*. 6th ed. New York: Wiley and Sons, 2002.
3. Wittekind Ch, Greene FL, Hutter RVP, et al. *TNM Atlas: Illustrated Guide to the TNM Classification of Malignant Tumours*. 5th ed. New Jersey: Wiley and Sons Inc, 2005.

Benign Tumors

1. Eveson JW, Kusafuka K, Stenman G et al. Pleomorphic adenoma. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:254–258.
2. Eveson JW, Cawson RA. Salivary gland tumors: A review of 2410 cases with particular reference to histologic types, site, age, and sex distribution. *J Pathol* 1985; 146(1):51–58.
3. Spiro RH. Salivary neoplasms: Overview of a 35 year experience with 2,807 patients. *Head Neck Surg* 1986; 8(3):177–184.
4. Eneroth CM. Salivary gland tumors in the parotid gland, submandibular gland and the palate region. *Cancer* 1971; 27(6):1415–1418.
5. Waldron CA, El-Mofty S, Gnepp DR. Tumors of the intraoral minor salivary glands: A demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* 1988; 66(3):323–333.
6. Waldron CA. Mixed tumor (pleomorphic adenoma) and myoepithelioma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:165–186.
7. Bouquot JE, Kurland LT, Weiland LH. Primary salivary epithelial neoplasms in the Rochester, Minnesota population. *J Dent Res* 1979; 58:419 (abstr).
8. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg* 1999; 120(6):834–840.
9. Uquz MZ, Onal K, Demiray U, et al. Tumoral mass presenting in the nasomalar region arising from the lateral nasal wall: pleomorphic adenoma. *Eur Arch Otorhinolaryngol* 2007; 264(11):1377–1379.
10. Berenholz L, Kessler A, Segal S. Massive pleomorphic adenoma of the maxillary sinus. A case report. *Int J Oral Maxillofac Surg* 1998; 27(5):372–373.
11. Heffner DK. Sinonasal and laryngeal salivary gland lesions. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:544–559.
12. Seifert G, Donath K. Multiple tumours of the salivary glands - terminology and nomenclature. *Eur J Cancer B Oral Oncol* 1996; 32(1):3–7.
13. Farina A, Pelucchi S, Carinci F. Evidence of bimodal distribution of age in patients affected by pleomorphic adenoma of the parotid gland. *Oral Oncol* 1997; 33(4):288–289.
14. Cameron JM. Familial incidence of inverted question mark mixed salivary tumours'. *Scott Med J* 1959; 4:455–456.
15. Ahn MS, Hayashi GM, Hilsinger RL Jr., et al. Familial mixed tumors of the parotid gland. *Head Neck* 1999; 21(8):772–775.
16. Hayter JP, Robertson JM. Familial occurrence of pleomorphic adenoma of the parotid gland. *Br J Oral Maxillofac Surg* 1990; 28(5):333–334.
17. Klausner RD, Handler SD. Familial occurrence of pleomorphic adenoma. *Int J Pediatr Otorhinolaryngol* 1994; 30(3):205–210.
18. Okura M, Hiranuma T, Shirasuna K, et al. Pleomorphic adenoma of the sublingual gland: report of a case. *J Oral Maxillofac Surg* 1996; 54(3):363–366.
19. Pesavento G, Ferlito A. Benign mixed tumor of heterotopic salivary gland tissue in upper neck. Report of a case with review of the literature on heterotopic salivary gland tissue. *J Laryngol* 1976; 90(6):577–584.
20. Shinohara M, Ikebe T, Nakamura S, et al. Multiple pleomorphic adenomas arising in the parotid and submandibular lymph nodes. *Br J Oral Maxillofac Surg* 1996; 34(6):515–519.
21. Feigin GA, Robinson B, Marchevsky A. Mixed tumor of the mediastinum. *Arch Pathol Lab Med* 1986; 110(1):80–81.
22. Ojha J, Bhattacharyya I, Islam MN, et al. Intraosseous pleomorphic adenoma of the mandible: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(2):e21–e26.
23. Surana R, Moloney R, Fitzgerald RJ. Tumours of heterotopic salivary tissue in the upper cervical region in children. *Surg Oncol* 1993; 2(2):133–136.
24. Moran CA. Primary salivary gland-type tumors of the lung. *Semin Diagn Pathol* 1995; 12(2):106–122.
25. Hampton TA, Scheithauer BW, Rojiani AM, et al. Salivary gland-like tumors of the sellar region. *Am J Surg Pathol* 1997; 21(4):424–434.
26. Porter N, Sandhu A, O'Connell TB, et al. Pleomorphic adenoma of the palpebral lobe of the lacrimal gland. *Otolaryngol Head Neck Surg* 2007; 136(2):328–329.
27. Cuadros CL, Ryan SS, Miller RE. Benign mixed tumor (pleomorphic adenoma) of the breast: Ultrastructural study and review of the literature. *J Surg Oncol* 1987; 36(1):58–63.
28. Hughes KV III, Olsen KD, McCaffrey TV. Parapharyngeal space neoplasms. *Head Neck* 1995; 17(2):124–130.
29. Buenting JE, Smith TL, Holmes DK. Giant pleomorphic adenoma of the parotid gland: Case report and review of the literature. *Ear Nose Throat J* 1998; 77(8):634–640.
30. Lee PS, Sabbath-Solitare M, Redondo TC, et al. Molecular evidence that the stromal and epithelial cells in pleomorphic adenomas of salivary gland arise from the same origin: clonal analysis using human androgen receptor gene (HUMARA) assay. *Hum Pathol* 2000; 31(4):498–503.
31. Webb AJ, Eveson JW. Pleomorphic adenomas of the major salivary glands: a study of the capsular form in relation to surgical management. *Clin Otolaryngol Allied Sci* 2001; 26(2):134–142.
32. Patey DH, Thackray AC. The treatment of parotid tumours in the light of a pathological study of parotidectomy material. *Br J Surg* 1958; 45(193):477–487.
33. Lam KH, Wei WI, Ho HC, et al. Whole organ sectioning of mixed parotid tumors. *Am J Surg* 1990; 160(4):377–381.

34. Takeda Y. An immunohistochemical study of bizarre neoplastic cells in pleomorphic adenoma: its cytological nature and proliferative activity. *Pathol Int* 1999; 49(2):993-999.
35. Tandler B. Amyloid in a pleomorphic adenoma of the parotid gland. Electron microscopic observations. *J Oral Pathol* 1981; 10(3):158-163.
36. Lomax-Smith JD, Azzopardi JG. The hyaline cell: A distinctive feature of "mixed" salivary tumours. *Histopathol* 1978; 2(2):77-92.
37. Palmer TJ, Gleeson MJ, Eveson JW, et al. Oncocytic adenomas and oncocytic hyperplasia of salivary glands: a clinicopathological study of 26 cases. *Histopathology* 1990; 16(5):487-493.
38. Di Palma S, Lambros MB, Savage K, et al. Oncocytic change in pleomorphic adenoma: molecular evidence in support of an origin in neoplastic cells. *J Clin Pathol* 2007; 60(5):492-499.
39. Auclair PL, Ellis GL. Atypical features in salivary gland mixed tumors: Their relationship to malignant transformation. *Mod Pathol* 1996; 9(6):652-657.
40. Ng WK, Ma L. Pleomorphic adenoma with extensive lipometaplasia. *Histopathology* 1995; 27(3):285-288.
41. Seifert G, Donath K, Schäfer R. Lipomatous pleomorphic adenoma of the parotid gland. Classification of lipomatous tissue in salivary glands. *Pathol Res Pract* 1999; 195(4): 247-252.
42. Ide F, Kusama K. Myxolipomatous pleomorphic adenoma: an unusual oral presentation. *J Oral Pathol Med* 2004; 33(1):53-55.
43. Allen CM, Damm D, Neville B, et al. Necrosis in benign salivary gland neoplasms. Not necessarily a sign of malignant transformation. *Oral Surg Oral Med Oral Pathol* 1994; 78(4):455-461.
44. Behzatoglu K, Bahadir B, Huq GE, et al. Spontaneous infarction of a pleomorphic adenoma in parotid gland: diagnostic problems and review. *Diagn Cytopathol* 2005; 32(6):367-369.
45. Chen YK, Lin CC, Lai S, et al. Pleomorphic adenoma with extensive necrosis: report of two cases. *Oral Dis* 2004; 10(1): 54-59.
46. Dardick I, van Nostrand AWP, Phillips MJ. Histogenesis of salivary gland pleomorphic adenoma (mixed tumor) with an evaluation of the role of the myoepithelial cell. *Hum Pathol* 1982; 13(1):60-75.
47. Donath K, Seifert G. Tumour-simulating squamous cell metaplasia (SCM) in necrotic areas of salivary gland tumours. *Pathol Res Pract* 1997; 193(1):689-693.
48. Lam KY, Ng IOL, Chan GSW. Palatal pleomorphic adenoma with florid squamous metaplasia: A potential diagnostic pitfall. *J Oral Pathol Med* 1998; 27(8):407-410.
49. Li S, Baloch ZW, Tomaszewski JE, LiVolsi VA. Worrisome histologic alterations following fine-needle aspiration of benign parotid lesions. *Arch Pathol Lab Med* 2000; 124(1): 87-91.
50. Batsakis JG. Recurrent mixed tumors. *Ann Otol Rhinol Laryngol* 1986; 95(5):543-544.
51. Gnepp DR, Schroeder W, Heffner D. Synchronous tumors arising in a single major salivary gland. *Cancer* 1989; 63(6):1219-1224.
52. Ishikawa N, Hashimoto K. Bilateral pleomorphic adenoma of the parotid gland. *J Otolaryngol* 1998; 27(2):94-96.
53. Coleman H, Altini M. Intravascular tumour in intra-oral pleomorphic adenomas: A diagnostic and therapeutic dilemma. *Histopathol* 1999; 35(5):439-444.
54. Burns BF, Dardick I, Parks WR. Intermediate filament expression in normal parotid glands and pleomorphic adenomas. *Virchows Arch A Pathol Anat Histopathol* 1988; 413(2):103-112.
55. Ogawa Y, Kishino M, Atsumi Y, et al. Plasmacytoid cells in salivary-gland pleomorphic adenomas: evidence of luminal cell differentiation. *Virchows Arch* 2003; 443(5):625-634.
56. Saveria AT, Gown AM, Zarbo RJ. Immunolocalization of three novel smooth muscle specific proteins in salivary gland pleomorphic adenoma: Assessment of the morphogenetic role of myoepithelium. *Mod Pathol* 1997; 10(11): 1093-1100.
57. Mori M, Yamada K, Tanaka T, et al. Multiple expression of keratins, vimentin, and S-100 protein in pleomorphic salivary adenomas. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1990; 58(6):435-444.
58. Furuse C, Sousa SO, Nunes FD, et al. Myoepithelial cell markers in salivary gland neoplasms. *Int J Surg Pathol* 2005; 13(1):57-65.
59. Bilal H, Handra-Luca A, Bertrand JC, et al. P63 is expressed in basal and myoepithelial cells of human normal and tumor salivary gland tissues. *J Histochem Cytochem* 2003; 51(2):133-139.
60. Andreadis D, Epivatianos A, Pouloupoulos A. Detection of C-KIT (CD117) molecule in benign and malignant salivary gland tumours. *Oral Oncol* 2006; 42(1):57-65.
61. Morinaga S, Nakajima T, Shimosato Y. Normal and neoplastic myoepithelial cells in salivary glands: an immunohistochemical study. *Hum Pathol* 1987; 18(12):1218-1226.
62. Kusafuka K, Yamaguchi A, Kayano T, et al. Immunohistochemical localization of members of the transforming growth factor (TGF)-beta superfamily in normal human salivary glands and pleomorphic adenomas. *J Oral Pathol Med* 2001; 30(7):413-420.
63. Kusafuka K, Yamaguchi A, Kayano T, et al. Expression of bone morphogenetic proteins in salivary pleomorphic adenomas. *Virchows Arch* 1998; 432(3):247-253.
64. Kusafuka K, Yamaguchi A, Kayano T, et al. Immunohistochemical localization of the bone morphogenetic protein-6 in salivary pleomorphic adenomas. *Pathol Int* 1999; 49(12): 1023-1027.
65. Kusafuka K, Hiraki Y, Shukunami C, et al. Cartilage-specific matrix protein chondromodulin-I is associated with chondroid formation in salivary pleomorphic adenomas: immunohistochemical analysis. *Am J Pathol* 2001; 158(4):1465-1472.
66. Mark J, Dahlenfors R, Wedell B. Impact of the in vitro technique used on the cytogenetic patterns in pleomorphic adenomas. *Cancer Genet Cytogenet* 1997; 95(1):9-15.
67. Bullerdiek J, Wobst G, Meyer-Bolte K, et al. Cytogenetic subtyping of 220 salivary gland pleomorphic adenomas: correlation to occurrence, histological subtype, and in vitro cellular behavior. *Cancer Genet Cytogenet* 1993; 65(1): 27-31.
68. Åström AK, Voz ML, Kas K, et al. Conserved mechanism of PLAG1 activation in salivary gland tumors with and without chromosome 8q12 abnormalities: identification of SII as a new fusion partner gene. *Cancer Res* 1999; 59(4): 918-923.
69. Kas K, Voz ML, Röijer E, et al. Promoter swapping between the genes for a novel zinc finger protein and beta-catenin in pleomorphic adenomas with t(3;8)(p21;q12) translocations. *Nat Genet* 1997; 15(2):170-174.
70. Voz ML, Åström AK, Kas K, et al. The recurrent translocation t(5;8)(p13;q12) in pleomorphic adenomas results in upregulation of PLAG1 gene expression under control of the LIFR promoter. *Oncogene* 1998; 16(11):1409-1416.
71. Voz ML, Agten NS, Van de Ven WJ, et al. PLAG1, the main translocation target in pleomorphic adenoma of the salivary glands, is a positive regulator of IGF-II. *Cancer Res* 2000; 60(1):106-113.
72. Martins C, Fonseca I, Roque L, et al. PLAG1 gene alterations in salivary gland pleomorphic adenoma and carcinoma ex-pleomorphic adenoma: a combined study using chromosome banding, in situ hybridization and immunocytochemistry. *Mod Pathol* 2005; 18(8):1048-1055.

73. Stenman G, Sandros J, Mark J, et al. High p21RAS expression levels correlate with chromosome 8 rearrangements in benign human mixed salivary gland tumors. *Genes Chromosomes Cancer* 1989; 1(1):59–66.
74. Milasin J, Pujić N, Dedović N, et al. H-ras gene mutations in salivary gland pleomorphic adenomas. *Int J Oral Maxillofac Surg* 1993; 22(6):359–361.
75. Stenman G, Sandros J, Nordkvist A, et al. Expression of the ERBB2 protein in benign and malignant salivary gland tumors. *Genes Chromosomes Cancer* 1991; 3(2):128–135.
76. Rosa JC, Felix A, Fonseca I, et al. Immunoexpression of c-erbB-2 and p53 in benign and malignant salivary neoplasms with myoepithelial differentiation. *J Clin Pathol* 1997; 50(8):661–663.
77. Nordkvist A, Röijer E, Bang G, et al. Expression and mutation patterns of p53 in benign and malignant salivary gland tumors. *Int J Oncol* 2000; 16(3):477–483.
78. Weber A, Langhanki L, Schütz A, et al. Expression profiles of p53, p63, and p73 in benign salivary gland tumors. *Virchows Arch* 2002; 441(5):428–436.
79. Martinelli M, Martini F, Rinaldi E, et al. Simian virus 40 sequences and expression of the viral large T antigen oncoprotein in human pleomorphic adenomas of parotid glands. *Am J Pathol* 2002; 161(4):1127–1133.
80. Chandan VS, Wilbur D, Faquin WC, et al. Is c-kit (CD117) immunolocalization in cell block preparations useful in the differentiation of adenoid cystic carcinoma from pleomorphic adenoma? *Cancer* 2004; 102(4):207–209.
81. Stennert E, Wittekindt C, Klussmann JP, et al. Recurrent pleomorphic adenoma of the parotid gland: a prospective histopathological and immunohistochemical study. *Laryngoscope* 2004; 114(1):158–163.
82. Zbären P, Tschumi I, Nuyens M, et al. Recurrent pleomorphic adenoma of the parotid gland. *Am J Surg* 2005; 189(2):203–207.
83. Hickman RE, Cawson RA, Duffy SW. The prognosis of specific types of salivary gland tumors. *Cancer* 1984; 54(8):1620–1624.
84. Myssiorek D, Ruah CB, Hybels RL. Recurrent pleomorphic adenomas of the parotid gland. *Head Neck* 1990; 12(4):332–336.
85. McGregor AD, Burgoyne M, Tan KC. Recurrent pleomorphic salivary adenoma: The relevance of age at first presentation. *Br J Plast Surg* 1988; 41(2):177–181.
86. Henriksson G, Westrin KM, Carlsoo B, et al. Recurrent primary pleomorphic adenomas of salivary gland origin: Intraoperative rupture, histopathologic features, and pseudopodia. *Cancer* 1998; 82(4):617–620.
87. Renehan A, Gleave EN, Hancock BD, et al. Long term follow up of over 1000 patients with salivary gland tumours treated in a single centre. *Br J Surg* 1996; 83(12):1750–1754.
88. Leverstein H, van der Wal JE, Tiwari RM, et al. Surgical management of 246 previously untreated pleomorphic adenomas of the parotid gland. *Br J Surg* 1997; 84(3):399–403.
89. Debets JM, Munting JD. Parotidectomy for parotid tumours: 19-year experience from The Netherlands. *Br J Surg* 1992; 79(11):1159–1161.
90. O'Brien CJ. Current management of benign parotid tumors—the role of limited superficial parotidectomy. *Head Neck* 2003; 25(11):946–952.
91. Ghosh S, Panarese A, Bull PD, et al. Marginally excised parotid pleomorphic salivary adenomas: risk factors for recurrence and management. A 12.5-year mean follow-up study of histologically marginal excisions. *Clin Otolaryngol Allied Sci* 2003; 28(3):262–266.
92. Bradley PJ. Pleomorphic salivary adenoma of the parotid gland: which operation to perform? *Curr Opin Otolaryngol Head Neck Surg* 2004; 12(2):69–70.
93. Witt RL. The significance of the margin in parotid surgery for pleomorphic adenoma. *Laryngoscope* 2002; 112(5):2141–2154.
94. Carr RJ, Bowerman JE. A review of tumours of the deep lobe of the parotid salivary gland. *Br J Oral Maxillofac Surg* 1986; 24(3):155–168.
95. Hamada T, Matsukita S, Goto M, et al. Mucin expression in pleomorphic adenoma of salivary gland: a potential role for MUC1 as a marker to predict recurrence. *J Clin Pathol* 2004; 57(8):813–821.
96. Laskawi R, Schott T, Schröder M. Recurrent pleomorphic adenomas of the parotid gland: Clinical evaluation and long-term follow-up. *Br J Oral Maxillofac Surg* 1998; 36(1):48–51.
97. Yugueros P, Goellner JR, Petty PM, et al. Treating recurrence of parotid benign pleomorphic adenomas. *Ann Plast Surg* 1998; 40(6):573–576.
98. Mendenhall WM, Mendenhall CM, Werning JW, et al. Salivary gland pleomorphic adenoma. *Am J Clin Oncol* 2008; 31(1):95–99.

Myoepithelioma

1. Cardesa A, Alos L. Myoepithelioma. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:259–260.
2. Ellis GL, Auclair PL. Myoepithelioma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:57–68.
3. Scuibba JJ, Brannon RB. Myoepithelioma of salivary glands: Report of 23 cases. *Cancer* 1982; 49(3):562–572.
4. Dardick I, Thomas MJ, van Nostrand AWP. Myoepithelioma—new concepts of histology and classification: A light and electron microscopic study. *Ultrastruct Pathol* 1989; 13(2–3):187–224.
5. Dardick I. Myoepithelioma: Definitions and diagnostic criteria. *Ultrastruct Pathol* 1995; 19(5):335–345.
6. Barnes L, Appel BN, Perez H, et al. Myoepitheliomas of the head and neck: Case report and review. *J Surg Oncol* 1985; 28(1):21–28.
7. Simpson RH, Jones H, Beasley P. Benign myoepithelioma of the salivary glands: A true entity? *Histopathology* 1995; 27(1):1–9.
8. Kutzner H, Mentzel T, Kaddu S, et al. Cutaneous myoepithelioma: an under-recognized cutaneous neoplasm composed of myoepithelial cells. *Am J Surg Pathol* 2001; 25(3):348–355.
9. Veeramachaneni R, Gulick J, Halldorsson AO, et al. Benign myoepithelioma of the lung: a case report and review of the literature. *Arch Pathol Lab Med* 2001; 125(11):1494–1496.
10. Hornick JL, Fletcher CDM. Myoepithelial tumors of soft tissue: A clinicopathologic and immunohistochemical study of 101 cases with an evaluation of prognostic parameters. *Am J Surg Pathol* 2003; 27(9):1183–1196.
11. Nagao T, Sugano I, Ishida Y, et al. Salivary gland malignant myoepithelioma: A clinicopathologic and immunohistochemical study of 10 cases. *Cancer* 1998; 83(7):1292–1299.
12. Skálová A, Leivo I, Michal M, et al. Analysis of collagen isotypes in crystalloid structures of salivary gland tumors. *Hum Pathol* 1992; 23(7):748–754.
13. Skálová A, Stárek I, Simpson RH, et al. Spindle cell myoepithelial tumours of the parotid gland with extensive lipomatous metaplasia. A report of four cases with immunohistochemical and ultrastructural findings. *Virchows Arch* 2001; 439(6):762–767.
14. Franquement DW, Mills SE. Plasmacytoid monomorphic adenoma of salivary glands: Absence of myogenous

- differentiation and comparison to spindle cell myoepithelioma. *Am J Surg Pathol* 1993; 17(2):146–153.
15. Skálová A, Michal M, Ryska A, et al. Oncocytic myoepithelioma and pleomorphic adenoma of the salivary glands. *Virchows Arch* 1999; 434(6):537–546.
 16. Mori M, Ninomiya T, Okada Y, et al. Myoepitheliomas and myoepithelial adenomas of salivary gland origin: Immunohistochemical evaluation of filament proteins, S-100a and b, glial fibrillary acidic proteins, neuron-specific enolase, and lactoferrin. *Pathol Res Pract* 1989; 184(2):168–178.
 17. Takai Y, Dardick I, MacKay A, et al. Diagnostic criteria for neoplastic myoepithelial cells in pleomorphic adenomas and myoepitheliomas: Immunocytochemical detection of muscle-specific actin, cytokeratin 14, vimentin and glial fibrillary acidic protein. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 79(3):330–341.
 18. Alós L, Cardesa A, Bombi JA, et al. Myoepithelial tumors of salivary glands: A clinicopathologic, immunohistochemical, ultrastructural, and flow-cytometric study. *Semin Diagn Pathol* 1996; 13(2):138–147.
 19. Saveria AT, Zarbo RJ. Defining the role of myoepithelium in salivary gland neoplasia. *Adv Anat Pathol* 2004; 11(2):69–85.
 20. Bombi JA, Alós L, Rey MJ, et al. Myoepithelial carcinoma arising in a benign myoepithelioma: immunohistochemical, ultrastructural, and flow-cytometric study. *Ultrastruct Pathol* 1996; 20(2):145–154.

Basal Cell Adenoma

1. Seifert G. Classification and differential diagnosis of clear and basal cell tumors of the salivary glands. *Semin Diagn Pathol* 1996; 13(2):95–103.
2. Kleinsasser O, Klein HJ. Basalzelladenome der Speicheldrüsen. *Archiv Klin Exper Ohren- Nasen- und Kehlkopfheilk* 1967; 189:302–316.
3. Thackray AC, Sobin LH. World Health Organization International Histological Classification of Tumours: Histological Typing of Salivary Gland Tumours. Berlin: Springer-Verlag, 1972.
4. Crumpler C, Scharfenberg JC, Reed RJ. Monomorphic adenomas of salivary glands: Trabecular-tubular, canalicular, and basaloid variants. *Cancer* 1976; 38(1):193–200.
5. Batsakis JG, Brannon RB, Sciubba JJ. Monomorphic adenomas of major salivary glands: A histologic study of 96 tumours. *Clin Otolaryngol* 1981; 6(2):129–143.
6. Gardner DG, Daley TD. The use of the terms monomorphic adenoma, basal cell adenoma, and canalicular adenoma as applied to salivary gland tumors. *Oral Surg Oral Med Oral Pathol* 1983; 56(6):608–615.
7. Chaudhry AP, Cutler LS, Satchidanand S, et al. Monomorphic adenomas of the parotid glands: Their ultrastructure and histogenesis. *Cancer* 1983; 52(1):112–120.
8. Batsakis JG, Luna MA, El Naggar AK. Basaloid monomorphic adenomas. *Ann Otol Rhinol Laryngol* 1991; 100(8):687–690.
9. Seifert G, Sobin LH. World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours. 2nd ed. Berlin: Springer-Verlag, 1991.
10. de Araujo VC. Basal cell adenoma. In: Barnes L, Eveson JW, Reichart P, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press, 2005:261–262.
11. Ellis GL, Auclair PLB. Basal cell adenoma. *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:80–94.
12. Ferreiro JA. Canalicular adenoma. In: Barnes L, Eveson JW, Reichart P, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press, 2005:267.
13. Daley TD, Gardner DG, Smout MS. Canalicular adenoma: Not a basal cell adenoma. *Oral Surg Oral Med Oral Pathol* 1984; 57(2):181–188.
14. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies of basal cell adenoma of the parotid gland. *Cancer* 1982; 50(4):736–745.
15. Seifert G, Donath K. The congenital basal cell adenoma of salivary glands: Contribution to the differential diagnosis of congenital salivary gland tumours. *Virchows Archiv* 1997; 430(4):311–319.
16. Dardick I, Lytwyn A, Bourne AJ, et al. Trabecular and solid-cribriform types of basal cell adenoma: A morphologic study of two cases of an unusual variant of monomorphic adenoma. *Oral Surg Oral Med Oral Pathol* 1992; 73(1):75–83.
17. Dardick I, Daley TD, van Nostrand AWP. Basal cell adenoma with myoepithelial-derived “stroma”: A new major salivary gland tumor entity. *Head Neck Surg* 1986; 8(4):257–267.
18. Dardick I, Kahn HJ, van Nostrand AWP, et al. Salivary gland monomorphic adenoma: Ultrastructural, immunoperoxidase, and histogenetic aspects. *Am J Pathol* 1984; 115(3):334–348.
19. Ogawa I, Nikai H, Takata T, et al. The cellular composition of basal cell adenoma of the parotid. An immunohistochemical analysis. *Oral Surg Oral Med Oral Pathol* 1990; 70(5):619–626.
20. Ferreiro JA. Immunohistochemistry of basal cell adenoma of the major salivary glands. *Histopathology* 1994; 24(6):539–542.
21. Nagao T, Sugano I, Ishida Y, et al. Basal cell adenocarcinoma of the salivary glands: Comparison with basal cell adenoma through assessment of cell proliferation, apoptosis, and expression of p53 and bcl-2. *Cancer* 1998; 82(3):439–447.
22. Zarbo RJ, Prasad AR, Regezi JA, et al. Salivary gland basal cell and canalicular adenomas: Immunohistochemical demonstration of myoepithelial cell participation and morphogenetic considerations. *Arch Pathol Lab Med* 2000; 124(3):401–405.
23. Choi HR, Batsakis JG, Callender DL, et al. Molecular analysis of chromosome 16q regions in dermal analogue tumors of salivary glands: a genetic link to dermal cylindroma? *Am J Surg Pathol* 2002; 26(6):778–783.
24. Luna MA, Tortoledo ME, Allen M. Salivary dermal analogue tumors arising in lymph nodes. *Cancer* 1987; 59(6):1165–1169.
25. Schmidt KT, Ma A, Golberg R, et al. Multiple adnexal tumors and a parotid basal cell adenoma. *J Am Acad Dermatol* 1991; 25(5 pt2):960–964.
26. Jungehülsing M, Wagner M, Damm M. Turban tumour with involvement of the parotid gland. *J Laryngol Otol* 1999; 113(8):779–783.
27. Luna MA, Batsakis JG, Tortoledo ME, et al. Carcinomas ex monomorphic adenoma of salivary glands. *J Laryngol Otol* 1989; 103(8):756–759.
28. Hyman BA, Scheithauer BW, Weiland LH, et al. Membranous basal cell adenoma of the parotid gland: Malignant transformation in a patient with multiple dermal cylindromas. *Arch Pathol Lab Med* 1988; 112(2):209–211.
29. Nagao T, Ishida Y, Sugano I, et al. Carcinoma in basal cell adenoma of the parotid gland. *Pathol Res Pract* 1997; 193(3):171–178.
30. Yu GY, Ubsmuller J, Donath K. Membranous basal cell adenoma of the salivary gland: A clinicopathologic study of 12 cases. *Acta Otolaryngol* 1998; 118(4):588–593.

Warthin's Tumor

- Ma J, Chan JKC, Chow CW, et al. Lymphadenoma: a report of three cases of an uncommon salivary gland neoplasm. *Histopathology* 2002; 41(4):250–259.
- Simpson RHW, Eveson JW. Warthin tumour. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:263–265.
- Ellis GL, Auclair PL. Warthin's tumor (papillary cystadenoma lymphomatosum). In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:68–79.
- Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol* 1985; 146(1):51–58.
- Poulsen P, Jorgensen K, Grontved A. Benign and malignant neoplasms of the parotid gland: incidence and histology in the Danish county of Funen. *Laryngoscope* 1987; 97(1):102–104.
- Monk JS, Church JS. Warthin's tumor: a high incidence and no sex predominance in central Pennsylvania. *Arch Otolaryngol Head Neck Surg* 1992; 118(5):477–478.
- Chung YFA, Khoo MLC, Heng MKD, et al. Epidemiology of Warthin's tumour of the parotid gland in an Asian population. *Br J Surg* 1999; 86(5):661–664.
- Thomas KM, Hutt MS, Borgstein J. Salivary gland tumors in Malawi. *Cancer* 1980; 46(10):2328–2334.
- Yoo GH, Eisele DW, Askin FB, et al. Warthin's tumor: a 40-year experience at the Johns Hopkins Hospital. *Laryngoscope* 1994; 104(7):799–803.
- Eveson JW, Cawson RA. Warthin's tumor (cystadenolymphoma) of salivary glands. A clinicopathologic investigation of 278 cases. *Oral Surg Oral Med Oral Pathol* 1986; 61(3):256–262.
- Skerlavay MA, Gardner B, Nacastri AD. Warthin's tumor in two brothers. *Arch Pathol Lab Med* 1976; 100(9):508.
- Noyek AM, Pritzker KPH, Greyson ND, et al. Familial Warthin's tumor 1. Its synchronous occurrence in mother and son, 2. its association with cystic oncocytic metaplasia of the larynx. *J Otolaryngol* 1980; 9(1):90–96.
- Ellies M, Laskawi R, Arglebe C. Extraglandular Warthin's tumours: clinical evaluation and long-term follow-up. *Br J Oral Maxillofac Surg* 1998; 36(1):52–53.
- van derWal JE, Davids JJ, van der Waal I. Extraparotid Warthin's tumours – report of 10 cases. *Br J Oral Maxillofac Surg* 1993; 31(1):43–44.
- Foot FW, Frazell EL. Tumors of the major salivary glands. *Cancer* 1953; 6(6):1065–1113.
- Kawakami M, Ito K, Tanaka H, et al. Warthin's tumor of the nasopharynx: a case report. *Auris Nasus Larynx* 2004; 31(3):293–298.
- Bonavolonta G, Tranfa F, Staibano S, et al. Warthin tumor of the lacrimal gland. *Am J Ophthalmol* 1997; 124(6):857–858.
- Gnepp DR, Brandwein MS, Henley JD. Salivary and lacrimal glands. In: Gnepp DR, eds. *Diagnostic Surgical Pathology of the Head and Neck*. Philadelphia: WB Saunders, 2001:325–430.
- Maiorano E, Lo Muzio L, Favia G, et al. Warthin's tumour: a study of 78 cases with emphasis on bilaterality, multifocality and association with other malignancies. *Oral Oncol* 2002; 38(1):35–40.
- Lam KH, Ho HC, Ho CM, et al. Multifocal nature of adenolymphoma of the parotid. *Br J Surg* 1994; 81(11):1612–1614.
- White RR, Arm RN, Randall P. A large Warthin's tumor of the parotid: case report. *Plast Reconstr Surg* 1978; 61(3):452–454.
- Michaels L, Hellquist HB. Part F: Major salivary glands: Chapter 41 benign epithelial neoplasms. In: *Ear, Nose and Throat Histopathology*. 2nd ed. London: Springer-Verlag, 2001:470–490.
- McGurk FM, Main JH, Orr JA. Adenolymphoma of the parotid gland. *Br J Surg* 1970; 57(5):321–325.
- Eveson JW, Cawson RA. Infarcted ('infected') adenolymphomas. A clinicopathological study of 20 cases. *Clin Otolaryngol* 1989; 14(3):205–210.
- Maini S, Osborne JE. Ischaemic necrosis and facial palsy in Warthin's tumour of the parotid gland. *Auris Nasus Larynx* 2002; 29(1):99–101.
- Marioni G, de Filippis C, Gaio E, et al. Facial nerve paralysis secondary to Warthin's tumour of the parotid gland. *J Laryngol Otol* 2003; 117(6):511–513.
- Motoori K, Ueda T, Uchida Y, et al. Identification of Warthin tumor: magnetic resonance imaging versus salivary scintigraphy with technetium-99m pertechnetate. *J Comput Assist Tomogr* 2005; 29(4):506–512.
- Ebbs SR, Webb AJ. Adenolymphoma of the parotid: aetiology, diagnosis and treatment. *Br J Surg* 1992; 73(8):627–630.
- Pinkston JA, Cole P. Cigarette smoking and Warthin's tumor. *Am J Epidemiol* 1996; 144(2):183–187.
- Kotwall CA. Smoking as an etiologic factor in the development of Warthin's tumor of the parotid gland. *Am J Surg* 1992; 164(6):646–647.
- Peter Klussmann J, Wittekindt C, Florian Preuss S, et al. High risk for bilateral Warthin tumor in heavy smokers – review of 185 cases. *Acta Otolaryngol* 2006; 126(11):1213–1217.
- Lamellas J, Terry JH, Alfonso AE. Warthin's tumor: multicentricity and increasing incidence in women. *Am J Surg* 1987; 154(4):347–351.
- Yu GY, Liu XB, Li ZL, et al. Smoking and the development of Warthin's tumour of the parotid gland. *Br J Oral Maxillofac Surg* 1998; 36(3):183–185.
- Saku T, Hayashi Y, Takahara O, et al. Salivary gland tumors among atomic bomb survivors, 1950–1987. *Cancer* 1997; 79(8):1465–1475.
- Gallo O, Bocciolini C. Warthin's tumour associated with autoimmune diseases and tobacco use. *Acta Otolaryngol* 1997; 117(4):623–627.
- Santucci M, Gallo O, Calzolari A, et al. Detection of Epstein-Barr viral genome in tumor cells of Warthin's tumor of parotid gland. *Am J Clin Pathol* 1993; 100(6):662–665.
- Van Heerden WFP, Kraft K, Hemmer J, et al. Warthin's tumour is not an Epstein-Barr virus related disease. *Anti-cancer Res* 1999; 19(4B):2881–2884.
- Webb AJ, Farndon JR. Epidemiology of Warthin's tumour of the parotid gland in an Asian population. *Br J Surg* 2000; 87(5):681 (letter).
- Webb AJ, Eveson JW. Parotid Warthin's tumour Bristol Royal Infirmary (1985–1995): a study of histopathology in 33 cases. *Oral Oncol* 2002; 38(2):163–171.
- Di Palma S, Simpson RHW, Skálová A, et al. Metaplastic (infarcted) Warthin's tumour of the parotid gland: a possible consequence of fine needle aspiration biopsy. *Histopathology* 1999; 35(5):432–438.
- Kern SB. Necrosis of a Warthin's tumor following fine needle aspiration. *Acta Cytol* 1988; 32(2):207–208.
- Batsakis JG, Sneige N, El-Naggar AK. Fine-needle aspiration of salivary glands: its utility and tissue effects. *Ann Otol Rhinol Laryngol* 1992; 101(2 pt1):185–188.
- Li S, Baloch ZW, Tomaszewski JE, et al. Worrisome histologic alterations following fine-needle aspiration of benign parotid lesions. *Arch Pathol Lab Med* 2000; 124(1):87–91.

44. Sironi M, Claren R, Spinelli M, et al. Could Warthin's tumor become metaplastic after fine needle aspiration? *Acta Cytol* 2002; 46(2):436-438.
45. Rawson AJ, Horn RC Jr. Sebaceous glands and sebaceous gland-containing tumors of the parotid salivary gland; with a consideration of the histogenesis of papillary cystadenoma lymphomatosum. *Surgery* 1950; 27(1):93-101.
46. Seifert G, Bull HG, Donath K. Histological subclassification of the cystadenoma of the parotid gland: analysis of 275 cases. *Virchows Archiv A Pathol Anat Histol* 1980; 388(1): 13-38.
47. To EW, Tsang WM, Leung CY, et al. Warthin's tumor with multiple sarcoid-like granulomas: a case report. *J Oral Maxillofac Surg* 2002; 60(5):585-588.
48. Watanabe M, Nakayama T, Koduka Y, et al. Mycobacterium tuberculosis infection within Warthin's tumor: report of two cases. *Pathol Int* 2001; 51(10):797-801.
49. Simpson RHW, Sarsfield PTL. Benign and malignant lymphoid lesions of the salivary glands. *Curr Diagn Pathol* 1997; 4:91-99.
50. Auclair PL. Tumor-associated lymphoid proliferation in the parotid gland: a potential diagnostic pitfall. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):19-26.
51. Michal M, Skálová A, Simpson RHW, et al. Well differentiated acinic cell carcinoma of salivary glands associated with lymphoid rich stroma: clinicopathologic and immunohistochemical study using a proliferative marker MIB1. *Human Pathol* 1997; 28(5):595-600.
52. Aguirre JM, Echebarria MA, Martínez-Conde R, et al. Warthin tumor: a new hypothesis concerning its development. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85(1):60-63.
53. Honda K, Kashima K, Daa T, et al. Clonal analysis of the epithelial component of Warthin's tumor. *Human Pathol* 2000; 31(11):1377-1380.
54. Teymoortash A, Werner JA. Tissue that has lost its track: Warthin's tumour. *Virchows Arch* 2005; 446(6):585-588.
55. Suster S, Rosai J. Multilocular thymic cyst: an acquired reactive process: study of 18 cases. *Am J Surg Pathol* 1991; 15(5):388-398.
56. Schwerer MJ, Kraft K, Baczako K, et al. Cytokeratin expression and epithelial differentiation in Warthin's tumour and its metaplastic (infarcted) variant. *Histopathology* 2001; 39(4): 347-352.
57. Chu PG, Weiss LM. Cytokeratin 14 immunoreactivity distinguishes oncocytic tumour from its renal mimics: an immunohistochemical study of 63 cases. *Histopathology* 2001; 39(5):455-462.
58. Gurbuz YG, Yildiz K, Aydin Ö, et al. An unusual cytokeratin expression at Warthin's tumour: an immunohistochemical study of 30 cases of salivary gland tumours. *Histopathology* 2002; 41(suppl 1):106 (abstr).
59. Luna MA. Salivary glands. In: Pilch BZ, eds. *Head and Neck Surgical Pathology*. Philadelphia: Lippincott, Williams & Wilkins, 2001:284-349.
60. Chin KW, Billings KR, Ishiyama A, et al. Characterization of lymphocyte subpopulations in Warthin's tumor. *Laryngoscope* 1995; 105(9 pt1):928-933.
61. Kataoka R, Hyo Y, Hoshiya T, et al. Ultrastructural study of mitochondria in oncocytes. *Ultrastruct Pathol* 1991; 15(3): 231-239.
62. Dardick I, Claude A, Parks WR, et al. Warthin's tumor: an ultrastructural study and immunohistochemical study of basilar epithelium. *Ultrastruct Pathol* 1988; 12(4):419-432.
63. Lewis PD, Baxter P, Griffiths AP, et al. Detection of damage to the mitochondrial genome in the oncocytic cells of Warthin's tumour. *J Pathol* 2000; 191(1):274-281.
64. Hunt JL. Warthin tumors do not have microsatellite instability and express normal DNA mismatch repair proteins. *Arch Pathol Lab Med* 2006; 130(1):52-56.
65. Martins C, Cavaco B, Tonon G, et al. A study of *MECT1-MAML2* in mucoepidermoid carcinoma and Warthin's tumor of salivary glands. *J Mol Diagn* 2004; 6(3):205-210.
66. Enlund F, Behboudi A, Andren Y, et al. Altered Notch signaling resulting from expression of a *WAMTP1-MAML2* gene fusion in mucoepidermoid carcinomas and benign Warthin's tumors. *Exp Cell Res* 2004; 292(1):21-28.
67. Baloch ZW, LiVolsi VA. Warthin-like papillary carcinoma of the thyroid. *Arch Pathol Lab Med* 2000; 124(8):1192-1195.
68. Ludviková M, Ryška A, Korabecná M, et al. Oncocytic papillary carcinoma with lymphoid stroma (Warthin-like tumour) of the thyroid: a distinct entity with favourable prognosis. *Histopathology* 2001; 39(1):17-24.
69. Iwai H, Yamashita T. Local excision procedure for Warthin's tumor of the parotid gland. *Otolaryngol Head Neck Surg* 2005; 132(4):577-580.
70. Warnock GR. Papillary cystadenoma lymphomatosum (Warthin's tumor). In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:187-201.
71. Skálová A, Michal M, Nathanský Z. Epidermoid carcinoma arising in Warthin's tumour: a case study. *J Oral Pathol Med* 1994; 23(7):330-333.
72. Nagao T, Sugano I, Ishida Y, et al. Mucoepidermoid carcinoma arising in Warthin's tumour of the parotid gland: report of two cases with histopathological, ultrastructural and immunohistochemical studies. *Histopathology* 1998; 33(4):379-386.
73. Williamson JD, Simmons BH, el-Naggar A, et al. Mucoepidermoid carcinoma involving Warthin tumor. A report of five cases and review of the literature. *Am J Clin Pathol* 2000; 114(4):564-570.
74. Foschini MP, Malvi D, Betts CM. Oncocytic carcinoma arising in Warthin tumour. *Virchows Arch* 2005; 446(1): 88-90.
75. Fornelli A, Eusebi V, Pasquinelli G, et al. Merkel cell carcinoma of the parotid gland associated with Warthin tumour: report of two cases. *Histopathology* 2001; 39(4): 342-346.
76. Park CK, Manning JT Jr., Battifora H, et al. Follicle center lymphoma and Warthin tumor involving the same anatomic site. Report of two cases and review of the literature. *Am J Clin Pathol* 2000; 113(1):13-119.
77. Medeiros LJ, Rizzi R, Lardelli P, et al. Malignant lymphoma involving a Warthin's tumor: a case with immunophenotypic and gene rearrangement analysis. *Human Pathol* 1990; 21(9):974-977.
78. Melato M, Falconieri G, Fanin R, et al. Hodgkin's disease occurring in a Warthin's tumor: first case report. *Pathol Res Pract* 1986; 181(5):615-620.
79. Badve S, Evans G, Mady S, et al. A case of Warthin's tumour with coexistent Hodgkin's disease. *Histopathology* 1993; 22(5):280-281.
80. Pescarmona E, Perez M, Faraggiana T, et al. Nodal peripheral T-cell lymphoma associated with Warthin's tumour. *Histopathology* 2005; 47(2):221-222.
81. Marioni G, Marchese-Ragona R, Marino F, et al. MALT-type lymphoma and Warthin's tumour presenting in the same parotid gland. *Acta Otolaryngol* 2004; 124(3): 318-323.
82. Saxena A, Memaui B, Hasegawa W. Initial diagnosis of small lymphocytic lymphoma in parotidectomy for Warthin tumour, a rare collision tumour. *J Clin Pathol* 2005; 58(3):331-333.
83. Gnepp DR, Schroeder W, Heffner D. Synchronous tumors arising in a single major salivary gland. *Cancer* 1989; 63(6): 1219-1224.

84. Lefor AT, Ord RA. Multiple synchronous bilateral Warthin's tumors of the parotid glands with pleomorphic adenoma: case report and review of the literature. *Oral Surg Oral Med Oral Pathol* 1993; 76(3):319–324.
85. Slavin JL, Woodford NW, Busmanis I. Synchronous parotid myoepithelioma and Warthin's tumor. *Pathology* 1995; 27(2):199–200.

Oncocytoma

1. Huvos AG. Oncocytoma. In: Barnes L, Eveson JW, Reichart P, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:266.
2. Goode RK. Oncocytoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:225–237.
3. Brandwein MS, Huvos AG. Oncocytic tumors of major salivary glands. A study of 68 cases with follow-up of 44 patients. *Am J Surg Pathol* 1991; 15(6):514–528.
4. Thompson LD, Wenig BM, Ellis GL. Oncocytomas of the submandibular gland. A series of 22 cases and a review of the literature. *Cancer* 1996; 78(11):2281–2287.
5. Damm DD, White DK, Geissler RH Jr., et al. Benign solid oncocytoma of intraoral minor salivary glands. *Oral Surg Oral Med Oral Pathol* 1989; 67(1):84–86.
6. Kanazawa H, Furuya T, Murano A, et al. Oncocytoma of an intraoral minor salivary gland: report of a case and review of literature. *J Oral Maxillofac Surg* 2000; 58(8): 894–897.
7. Sugiyama T, Nakagawa T, Narita M, et al. Pedunculated oncocytic carcinoma in buccal mucosa: immunohistochemical and ultrastructural studies. *Oral Dis* 2006; 12(3):324–328.
8. Deutsch E, Elion A, Zelig S, et al. Synchronous bilateral oncocytoma of the parotid glands. A case report. *J Otol Rhinol Laryngol* 1984; 46(2):66–68.
9. Boley JO, Robinson DW. Bilateral oxyphilic granular cell adenoma of the parotid. Report of a case. *Arch Pathol* 1954; 58(6):564–567.
10. Blanck C, Eneroth CM, Jakobsson PA. Bilateral tumors of the parotid gland. *Opusc Med Bd* 1974; 19:30–33.
11. Ellis GL. "Clear cell" oncocytoma of the salivary gland. *Human Pathol* 1988; 19(7):862–867.
12. Davy CL, Dardick I, Hammond E, et al. Relationship of clear cell oncocytoma to mitochondrial-rich (typical) oncocytomas of parotid salivary gland. An ultrastructural study. *Oral Surg Oral Med Oral Pathol* 1994; 77(5):469–469.
13. Seifert G. Classification and differential diagnosis of clear and basal cell tumors of the salivary gland. *Semin Diagn Pathol* 1996; 13(2):95–103.
14. Sorensen M, Baunsgaard P, Frederiksen P, et al. Multifocal adenomatous oncocytic hyperplasia of the parotid gland. (Unusual clear cell variant in two female siblings.) *Pathol Res Pract* 1986; 181(2):254–257.
15. Gray SR, Cornog JL, Sei IS. Oncocytic neoplasms of salivary glands: A report of 15 cases including two malignant oncocytomas. *Cancer* 1976; 38(3):1306–1317.
16. Busuttill A. Oncocytic lesions of the upper respiratory tract. *J Laryngol Otol* 1976; 90(3):277–288.
17. Dardick I, Birek C, Lingen MW, et al. Differentiation and the cytomorphology of salivary gland tumors with specific reference to oncocytic metaplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 88(6): 691–701.
18. Palmer TJ, Gleeson MJ, Eveson JW, et al. Oncocytic adenomas and oncocytic hyperplasia of salivary glands: a clinicopathological study of 26 cases. *Histopathology* 1990; 16(5): 487–493.
19. Jahan-Parwar, Huberman RM, Donovan DT, et al. Oncocytic mucoepidermoid carcinoma of the salivary glands. *Am J Surg Pathol* 1999; 23(5):523–529.
20. Brannon RB, Willard CC. Oncocytic mucoepidermoid carcinoma of parotid gland origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(6):727–733.
21. Shick PC, Brannon RB. Oncocytoid artifact of the parotid gland. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86(6):720–722.
22. Said-Al-Naief N, Ivanov K, Jones M, et al. Granular cell tumor of the parotid. *Ann Diagn Pathol* 1999; 3(1):35–38.
23. Ellis GL, Auclair PL. Oncocytoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:103–114.
24. Blanck C, Eneroth CM, Jakobsson PA. Oncocytoma of the parotid gland: neoplasm or nodular hyperplasia? *Cancer* 1970; 25(4):919–925.

Canalicular Adenoma

1. Ferreiro JA. Canalicular adenoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:267.
2. Kratchovil FJ. Canalicular adenoma and basal cell adenoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:202–224.
3. Ellis GL, Auclair PL. Canalicular adenoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:95–103.
4. Daley TD, Gardner DG, Smout MS. Canalicular adenoma: not a basal cell adenoma. *Oral Surg Oral Med Oral Pathol* 1984; 57(2):181–188.
5. Nelson JF, Jacoway JR. Monomorphic adenoma (Canalicular type). Report of 29 cases. *Cancer* 1973; 31(6): 1511–1512.
6. Regezi JA, Lloyd RV, Zarbo RJ, et al. Minor salivary gland tumors. A histologic and immunohistochemical study. *Cancer* 1985; 55(1):108–115.
7. Suarez P, Hammond HL, Luna MA, et al. Palatal canalicular adenoma: report of 12 cases and review of the literature. *Ann Diagn Pathol* 1998; 2(4):224–228.
8. Rossiello R, Rossiello L, de Simone S, et al. Canalicular adenoma of the parotid gland: a case report. *Anticancer Res* 2003; 23(5b):4101–4103.
9. Philpott CM, Kendall C, Murty GE. Canalicular adenoma of the parotid gland. *J Laryngol Otol* 2005; 119(1):59–60.
10. Nelson ZL, Newman L, Loukota RA, et al. Bilateral multifocal canalicular adenomas of buccal minor salivary glands: a case report. *Br J Oral Maxillofac Surg* 1995; 33(5): 299–301.
11. Yoon AJ, Beller DE, Woo VL, et al. Bilateral canalicular adenomas of the upper lip. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102(3):341–343.
12. Rosseau A, Mock D, Dover DG, et al. Multiple canalicular adenomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 87(3):346–350.
13. Khullar SM, Best PV. Adenomatosis of minor salivary glands. Report of a case. *Oral Surg Oral Med Oral Pathol* 1992; 74(6):783–787.
14. Waldron CA, el-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* 1988; 66(3):323–333.
15. Allen CM, Damm D, Neville B, et al. Necrosis in benign salivary gland neoplasms. Not necessarily a sign of malignant transformation. *Oral Surg Oral Med Oral Pathol* 1994; 78(4):455–461.

16. Mintz GA, Abrams AM, Melrose RJ. Monomorphic adenomas of the major and minor salivary glands. Report of twenty-one cases and review of the literature. *Oral Surg Oral Med Oral Pathol* 1982; 53(4):375-386.
17. Zarbo RJ, Regezi JA, Batsakis JG. S-100 protein in salivary gland tumors: an immunohistochemical study of 129 cases. *Head Neck Surg* 1986; 8(4):268-275.
18. Pereira MC, Pereira AA, Hanemann JA. Immunohistochemical profile of canalicular adenoma of the upper lip: a case report. *Med Oral Patol Oral Cir Bucal* 2007; 12:E1-E3.
19. Ferreira JA. Immunohistochemical analysis of salivary gland canalicular adenoma. *Oral Surg Oral Med Oral Pathol* 1994; 78(6):761-765.
20. Machado de Sousa SO, Soares de Araujo N, Correa L, et al. Immunohistochemical aspects of basal cell adenoma and canalicular adenoma of salivary glands. *Oral Oncol* 2001; 37(4):365-368.
21. Zarbo RJ, Prasad AR, Regezi JA, et al. Salivary gland basal cell and canalicular adenomas: immunohistochemical demonstration of myoepithelial cell participation and morphogenetic considerations. *Arch Pathol Lab Med* 2000; 124(3):401-405.
22. Weber A, Langhanki L, Schutz A, et al. Expression profiles of p53, p63, and p73 in benign salivary gland tumors. *Virchows Arch* 2002; 441(5):428-436.
23. Seifert G, Donath K. Hybrid tumours of salivary glands. Definition and classification of five rare cases. *Eur J Cancer B Oral Oncol* 1996; 32B(4):251-259.
24. Fantasia JE, Neville BW. Basal cell adenomas of the minor salivary glands. A clinicopathologic study of seventeen new cases and a review of the literature. *Oral Surg Oral Med Oral Pathol* 1980; 50(5):433-440.
25. Harmse JL, Saleh HA, Odutoye T, et al. Recurrent canalicular adenoma of the minor salivary glands in the upper lip. *J Laryngol Otol* 1997; 111(10):985-987.
26. Mair IW, Stalsberg H. Basal cell adenomatosis of minor salivary glands of the upper lip. *Arch Otorhinolaryngol* 1988; 245(3):191-195.
27. Smullin SE, Fielding AF, Susarla SM, et al. Canalicular adenoma of the palate: case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; 98(1):32-36.

Sebaceous Adenoma

1. Gnepp DR. Sebaceous adenoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:268.
2. Seifert G, Miehke A, Haubrich J, et al. Diseases of the Salivary Glands. *Pathology-Diagnosis-Treatment-Facial Nerve Surgery*. Stuttgart: Georg Thieme Verlag, 1986; pp. 171, 215, 216.
3. Gnepp DR, Brannon R. Sebaceous neoplasms of salivary gland origin, report of 21 cases. *Cancer* 1984; 53(10):2155-2170.
4. Gnepp DR. Sebaceous neoplasms of salivary gland origin: a review. *Pathol Ann*, 1983; 18(pt 1):71-102.
5. de Vicente Rodriguez JC, Fresno Forcelledo MF, Gonzalez Garcia M, et al. Sebaceous adenoma of the parotid gland. *Med Oral Patol Oral Cir Bucal* 2006; 11:E446-E448.
6. Iezzi G, Rubini C, Fioroni M, et al. Sebaceous adenoma of the cheek. *Oral Oncol* 2002; 38(1):111-113.
7. Izutsu T, Kumamoto H, Kimizuka S, et al. Sebaceous adenoma in the retromolar region: report of a case with a review of the English literature. *Int J Oral Maxillofac Surg* 2003; 32(4):423-426.
8. Seifert G, Donath K. Hybrid tumours of salivary glands. Definition and classification of five rare cases. *Eur J Cancer Oral Oncol* 1996; 32B(4):251-259.

Lymphadenomas

1. Gnepp DR, Cheuk W, Chan JKC, et al. Lymphadenomas: sebaceous and non-sebaceous. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:269.
2. Gnepp DR. Sebaceous neoplasms of salivary gland origin: a review. *Pathol Annu* 1983; 18(pt 1):71-102.
3. Gnepp DR, Brannon R. Sebaceous neoplasms of salivary gland origin. Report of 21 cases. *Cancer* 1984; 53(10):2155-2170.
4. McGavran MH, Bauer WC, Ackerman LV. Sebaceous lymphadenoma of the parotid salivary gland. *Cancer* 1960; 13:1185-1187.
5. Rawson AJ, Horn RC Jr. Sebaceous glands and sebaceous gland-containing tumors of the parotid salivary gland; with a consideration of the histogenesis of papillary cystadenoma lymphomatosum. *Surgery* 1950; 27(1):93-101.
6. Auclair PL, Ellis GL, Gnepp DR. Other benign epithelial neoplasms. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:252-268.
7. Hayashi D, Tysome JR, Boyei E, et al. Sebaceous lymphadenoma of the parotid gland: report of two cases and review of the literature. *Acta Otorhinolaryngol Ital* 2007; 27(3):144-146.
8. Peel RL. Diseases of the salivary gland. In: Barnes L, eds. *Surgical Pathology of the Head and Neck*. New York: Marcel Dekker Inc., 2001:633-758.
9. Ellis GL, Auclair PL. Sebaceous lymphadenoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:133-136.
10. Auclair PL. Tumor-associated lymphoid proliferation in the parotid gland. A potential diagnostic pitfall. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):19-26.
11. Ma J, Chan JK, Chow CW, et al. Lymphadenoma: a report of three cases of an uncommon salivary gland neoplasm. *Histopathology* 2002; 41(4):342-350.
12. Kwon GY, Kim EJ, Go JH. Lymphadenoma arising in the parotid gland: a case report. *Yonsei Med J* 2002; 43(4):536-538.
13. Musthyala NB, Low SE, Seneviratne RH. Lymphadenoma of the salivary gland: a rare tumour. *J Clin Pathol* 2004; 57(9):1007.
14. Bos I, Meyer S, Merz H. [Lymphadenoma of the parotid gland without sebaceous differentiation. Immunohistochemical investigations]. *Pathologe* 2004; 25(1):73-78.
15. Chang JY, Hsiao CH. Lymphadenoma lacking sebaceous differentiation in the parotid gland. *J Formos Med Assoc* 2004; 103(6):459-462.
16. Yang S, Chen X, Wang L, et al. Non-sebaceous lymphadenoma of the salivary gland: case report with immunohistochemical investigation. *Virchows Arch* 2007; 450(5):595-599.
17. Dardick I, Thomas MJ. Lymphadenoma of parotid gland: two additional cases and a literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 105(4):491-494.

Ductal Papillomas

1. Brannon RB, Sciubba JJ. Ductal papillomas. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:270-272.

2. Ellis GL, Auclair PL. Ductal papillomas. In: Atlas of Tumor Pathology: Tumors of the Salivary Glands, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:120–130.
3. Abbey LM. Solitary intraductal papilloma of the minor salivary glands. *Oral Surg Oral Med Oral Pathol* 1975; 40(1):135–140.
4. King PH, Hill J. Intraductal papilloma of the parotid gland. *J Clin Pathol* 1993; 46(2):175–176.
5. Ishikawa T, Imada S, Ijuhin N. Intraductal papilloma of the anterior lingual salivary gland: case report and immunohistochemical study. *Int J Oral Maxillofac Surg* 1993; 22(2): 116–117.
6. Shiotani A, Kawaura M, Tanaka Y, et al. Papillary adenocarcinoma possibly arising from an intraductal papilloma of the parotid gland. *ORL J Otorhinolaryngol Relat Spec* 1994; 56(2):112–115.
7. Saleh HA, Abbarah T. Intraductal papilloma of the minor salivary gland involving the nasal cavity: is it a distinct histopathologic entity? *Otolaryngol Head Neck Surg* 1998; 118(6):850–852.
8. Nagao T, Sugano I, Matsuzaki O, et al. Intraductal papillary tumors of the major salivary glands: case reports of benign and malignant variants. *Arch Pathol Lab Med* 2000; 124(2):291–295.
9. Brannon RB, Sciubba JJ, Giulani M. Ductal papillomas of salivary gland origin: a report of 19 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 92(1):68–77.
10. Tanimoto H, Kaneshiro T, Yonezawa K, et al. Intraductal papilloma arising from Stensen's duct. *J Otolaryngol* 2005; 34(6):432–433.
11. Noseri H, Erden T, Toros S, et al. Intraductal papilloma of the parotid gland in a child. *Eur Arch Otorhinolaryngol* 2007; 264(11):1385–1386.
12. Brandwein-Gensler MS, Gnepp DR. Low-grade cribriform cystadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press, 2005:233.
13. Abrams AM, Finck FM. Sialadenoma papilliferum. *Cancer* 1969; 24(5):1057–1063.
14. Shirasuna K, Watatani K, Miyazaki T. Ultrastructure of sialadenoma papilliferum. *Cancer* 1984; 53(3):468–474.
15. Fantasia JE, Nocco CE, Lally ET. Ultrastructure of sialadenoma papilliferum. *Arch Pathol Lab Med* 1986; 110(6):523–527.
16. Pimentel MT, Lopez Amado M, Garcia Sarandesha A. Recurrent sialadenoma papilliferum of the buccal mucosa. *J Laryngol Otol* 1995; 109(8):787–790.
17. Maiorano E, Favia G, Ricco R. Sialadenoma papilliferum: an immunohistochemical study of five cases. *J Oral Pathol Med* 1996; 25(6):336–342.
18. Su JM, Hsu HK, Hsu PL, et al. Sialadenoma papilliferum of the esophagus. *Am J Gastroenterol* 1998; 93(3):461–462.
19. Argyres MI, Golitz LE. Sialadenoma papilliferum of the palate: case report and literature review. *J Cutan Pathol* 1999; 26(5):259–262.
20. Ubaidat MA, Robinson RA, Belding PJ, et al. Sialadenoma papilliferum of the hard palate: report of 2 cases and immunohistochemical evaluation. *Arch Pathol Lab Med* 2001; 125(12):1595–1597.
21. Bobos M, Hytioglou P, Karkavelas G, et al. Sialadenoma papilliferum of bronchus. *Virchows Arch* 2003; 443(5): 695–699.
22. Gomes AP, Sobral AP, Loducca SV, et al. Sialadenoma papilliferum: immunohistochemical study. *Int J Oral Maxillofac Surg* 2004; 33(6):621–624.
23. Shimoda M, Kameyama K, Morinaga S, et al. Malignant transformation of sialadenoma papilliferum of the palate: a case report. *Virchows Arch* 2004; 445(6):641–646.
24. Ponniah I. A rare case of sialadenoma papilliferum with epithelial dysplasia and carcinoma in situ. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(2): e27–e29.
25. Mahajan D, Khurana N, Setia N. Sialadenoma papilliferum in a young patient: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(3):e51–e54.
26. White DK, Miller AS, McDaniel RK, et al. Inverted ductal papilloma: a distinctive lesion of minor salivary gland. *Cancer* 1982; 49(3):519–524.
27. Clark DB, Priddy RW, Swanson AE. Oral inverted ductal papilloma. *Oral Surg Oral Med Oral Pathol* 1990; 69(4): 487–490.
28. Koutlas IG, Jessurun J, Iamaroon A. Immunohistochemical evaluation and in situ hybridization in a case of oral inverted ductal papilloma. *J Oral Maxillofac Surg* 1994; 52(5):503–506.
29. Huberland-Carrodegus C, Fornatora ML, Reich RF, et al. Detection of human papillomavirus DNA in oral inverted ductal papillomas. *J Clin Pathol* 2003; 56(12):910–913.
30. Cabov T, Macan D, Manojlović S, et al. Oral inverted ductal papilloma. *Br J Oral Maxillofac Surg* 2004; 42(1):75–77.
31. Kubota N, Suzuki K, Kawai Y, et al. Inverted ductal papilloma of minor salivary gland: case report with immunohistochemical study and literature review. *Pathol Int* 2006; 56(8):457–461.

Cystadenoma

1. Skálová A, Michal M. Cystadenoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Head and Neck. Lyon: IARC Press, 2005:273–274.
2. Auclair PL, Ellis GL, Gnepp DR. Other benign epithelial neoplasms. In: Ellis GL, Auclair PL, Gnepp DR, eds. Surgical Pathology of the Salivary Glands. Philadelphia: WB Saunders, 1991:252–268.
3. Ellis GL, Auclair PL. Cystadenoma. In: Atlas of Tumor Pathology: Tumors of the Salivary Glands. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:115–120.
4. Waldron CA, El-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* 1988; 66(3):323–333.
5. Loyola AM, de Araújo VC, de Sousa SO, et al. Minor salivary gland tumours. A retrospective study of 164 cases in a Brazilian population. *Eur J Cancer B Oral Oncol* 1995; 31B(3):197–201.
6. Toida M, Shimokawa K, Makita H, et al. Intraoral minor salivary gland tumors: a clinicopathological study of 82 cases. *Int J Oral Maxillofac Surg* 2005; 34(5):528–532.
7. Buchner A, Merrell PW, Carpenter WM. Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. *J Oral Pathol Med* 2007; 36(4):207–214.
8. Kroe DJ, Pitcock JA, Cocke EW. Oncocytic papillary cystadenoma of the larynx. Presentation of two cases. *Arch Pathol* 1967; 84(4):429–432.
9. Gnepp DR, Heffner DK. Mucosal origin of sinonasal tract adenomatous neoplasms. *Mod Pathol* 1989; 2(4): 365–371.
10. Alexis JB, Dembrow V. Papillary cystadenoma of a minor salivary gland. *J Oral Maxillofac Surg* 1995; 53(1):70–72.

11. Guccion JG, Redman RS, Calhoun NR, et al. Papillary cystadenoma of the palate: a case report and ultrastructural study. *J Oral Maxillofac Surg* 1997; 55(7):759-764.
12. Chaushu G, Buchner A, David R. Multiple oncocytic cysts with tyrosine-crystalloids in the parotid gland. *Hum Pathol* 1999; 30(2):237-239.
13. Skálová A, Leivo I, Wolf H, et al. Oncocytic cystadenoma of the parotid gland with tyrosine-rich crystals. *Pathol Res Pract* 2000; 196(12):849-851.
14. Matsuzaka K, Kokubu E, Takeda E, et al. Papillary cystadenoma arising from the upper lip: a case report. *Bull Tokyo Dent Coll* 2003; 44(4):213-216.
15. Michal M, Hrabal P, Skálová A. Oncocytic cystadenoma of the parotid gland with prominent signet-ring features. *Pathol Int* 1998; 48(8):629-633.
16. Auclair PL. Cystadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Head and Neck*. Lyon: IARC Press, 2005:232.
17. Brandwein-Gensler MS, Gnepp DR. Low-grade cribriform cystadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Head and Neck*. Lyon: IARC Press, 2005:233.
18. Delgado R, Klimstra D, Albores-Saavedra J. Low grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern. *Cancer* 1996; 78(5):958-967.
19. Michal M, Skálová A, Mukensnabl P. Micropapillary carcinoma of the parotid gland arising in mucinous cystadenoma. *Virchows Arch* 2000; 437(4):465-468.

Keratocystoma

1. Seifert G, Donath K, Jautzke G. Unusual choristoma of the parotid gland in a girl: a possible trichoadenoma. *Virchows Arch* 1999; 434(4):355-359.
2. Nagao T, Serizawa H, Iwaya K, et al. Keratocystoma of the parotid gland: a report of two cases of an unusual pathologic entity. *Mod Pathol* 2002; 15(9):1005-1010.
3. Lewis JE, Olsen KD. Squamous cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:245-246.
4. Eveson JW, Cawson RA. Infarcted (infected) adenolymphomas: a clinicopathological study of 20 cases. *Clin Otolaryngol* 1989; 14(3):205-210.
5. Schwerer MJ, Kraft K, Baczako K, et al. Cytokeratin expression and epithelial differentiation in Warthin's tumor and its metaplastic (infarcted) variant. *Histopathology* 2001; 39(4):347-352.
6. Abrams AM, Melrose RJ, Howell FV. Necrotizing sialometaplasia: a disease simulating malignancy. *Cancer* 1973; 32(1):130-135.
7. Brannon RB, Fowler CB, Hartman KS. Necrotizing sialometaplasia: a clinicopathologic study of sixty-nine cases and review of the literature. *Oral Surg Oral Med Oral Pathol* 1991; 72(3):317-325.
8. Sneige N, Batsakis JG. Necrotizing sialometaplasia. *Ann Otol Rhinol Laryngol* 1992; 101(3):282-284.
9. Pieterse AS, Seymour AE. Parotid cysts. An analysis of 16 cases and suggested classification. *Pathology* 1981; 13(2):225-234.
10. Moody AB, Avery CME, Harrison JD. Dermoid cyst of the parotid gland. *Int J Oral Maxillofac Surg* 1998; 27(6):461-462.

Malignant Tumors

Acinic Cell Carcinoma

1. Ellis G, Simpson RHW. Acinic cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:216-218.
2. Ellis GL, Auclair PL. Acinic cell adenocarcinoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:299-317.
3. Ellis GL, Auclair PL. Acinic cell adenocarcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:183-203.
4. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg* 1986; 8(3):177-184.
5. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol* 1985; 146(1):51-58.
6. Jang J, Kie JH, Lee SY, et al. Acinic cell carcinoma of the lacrimal gland with intracranial extension: a case report. *Ophthalm Plast Reconstr Surg* 2001; 17(6):454-457.
7. Crissman JD, Rosenblatt A. Acinous cell carcinoma of the larynx. *Arch Pathol Lab Med* 1978; 102(5):233-236.
8. Tsukayama S, Omura K, Kanehira E, et al. Acinic cell carcinoma of the trachea: report of a case. *Surg Today* 2004; 34(9):764-768.
9. Hara I, Ozeki S, Okamura K, et al. Central acinic cell carcinoma of the mandible. Case report. *J Craniomaxillofac Surg* 2003; 31(6):378-382.
10. Gnepp DR, Schroeder W, Heffner D. Synchronous tumors arising in a single major salivary gland. *Cancer* 1989; 63(6):1219-1224.
11. Delides A, Velegrakis G, Kontogeorgos G, et al. Familial bilateral acinic cell carcinoma of the parotid synchronous with pituitary adenoma: case report. *Head Neck* 2005; 27(9):825-828.
12. Nagao T, Sugano I, Ishida Y, et al. Hybrid carcinomas of the salivary glands: report of nine cases with clinicopathologic, immunohistochemical, and p53 gene alteration analysis. *Mod Pathol* 2002; 15(7):724-733.
13. Eneroth CM, Jakobsson PA, Blanck C. Acinic cell carcinoma of the parotid gland. *Cancer* 1966; 19(12):1761-1772.
14. Batsakis JG, Chinn EK, Weimert TA, et al. Acinic cell carcinoma: a clinicopathologic study of thirty-five cases. *J Laryngol Otol* 1979; 93(4):325-340.
15. Ellis GL, Corio RL. Acinic cell adenocarcinoma. A clinicopathologic analysis of 294 cases. *Cancer* 1983; 52(3):542-549.
16. Shapiro NL, Bhattacharyya N. Clinical characteristics and survival for major salivary gland malignancies in children. *Otolaryngol Head Neck Surg* 2006; 134(4):631-634.
17. Kessler A, Handler SD. Salivary gland neoplasms in children: a 10-year survey at the Children's Hospital of Philadelphia. *Int J Pediatr Otorhinolaryngol* 1994; 29(3):195-202.
18. Orvidas LJ, Kasperbauer JL, Lewis JE, et al. Pediatric parotid masses. *Arch Otolaryngol Head Neck Surg* 2000; 126(2):177-184.
19. Castro EB, Huvos AG, Strong EW, et al. Tumors of the major salivary glands in children. *Cancer* 1972; 29(2):312-317.
20. Depowski PL, Setzen G, Chui A, et al. Familial occurrence of acinic cell carcinoma of the parotid gland. *Arch Pathol Lab Med* 1999; 123(11):1118-1120.
21. Abrams AM, Cornyn J, Scofield HH, et al. Acinic cell adenocarcinoma of the major salivary glands. A clinicopathologic study of 77 cases. *Cancer* 1965; 18(9):1145-1162.

22. Chong GC, Beahrs OH, Woolner LB. Surgical management of acinic cell carcinoma of the parotid gland. *Surg Gynecol Obstet* 1974; 138(1):65-68.
23. Spiro RH, Huvois AG, Strong EW. Acinic cell carcinoma of salivary origin. A clinicopathologic study of 67 cases. *Cancer* 1978; 41(3):924-935.
24. Abrams AM, Melrose RJ. Acinic cell tumors of minor salivary gland origin. *Oral Surg Oral Med Oral Pathol* 1978; 46(2):220-233.
25. Colmenero C, Patron M, Sierra I. Acinic cell carcinoma of the salivary glands. A review of 20 new cases. *J Cranio-maxillofac Surg* 1991; 19(6):260-266.
26. Ellis GL. Clear cell neoplasms in salivary glands: clearly a diagnostic challenge. *Ann Diagn Pathol* 1998; 2(1):61-78.
27. Chaudhry AP, Cutler LS, Leifer C, et al. Histogenesis of acinic cell carcinoma of the major and minor salivary glands. An ultrastructural study. *J Pathol* 1986; 148(4):307-320.
28. Whitlatch SP. Psammoma bodies in fine-needle aspiration biopsies of acinic cell tumor. *Diagn Cytopathol* 1986; 2(3):268-269.
29. Mukunyadzi P, Bardales RH, Palmer HE, et al. Tissue effects of salivary gland fine-needle aspiration. Does this procedure preclude accurate histologic diagnosis? *Am J Clin Pathol* 2000; 114(5):741-745.
30. Auclair PL. Tumor-associated lymphoid proliferation in the parotid gland. A potential diagnostic pitfall. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):19-26.
31. Michal M, Skálová A, Simpson RHW, et al. Well differentiated acinic cell carcinoma of salivary glands associated with lymphoid stroma. *Hum Pathol* 1997; 28(5):595-600.
32. Stanley RJ, Weiland LH, Olsen KD, et al. Dedifferentiated acinic cell (acinous) carcinoma of the parotid gland. *Otolaryngol Head Neck Surg* 1988; 98(2):155-161.
33. Henley JD, Geary WA, Jackson C, et al. Dedifferentiated acinic cell carcinoma of the parotid gland: a distinctive rarely described entity. *Hum Pathol* 1997; 28(7):869-873.
34. Di Palma S, Corletto V, Lavarino C, et al. Unilateral aneuploid dedifferentiated acinic cell carcinoma associated with bilateral low grade diploid acinic cell carcinoma of the parotid gland. *Virchows Arch* 1999; 434(4):361-365.
35. Timon CI, Dardick I. The importance of dedifferentiation in recurrent acinic cell carcinoma. *J Laryngol Otol* 2001; 115(8):639-644.
36. Piana S, Cavazza A, Pedroni C, et al. Dedifferentiated acinic cell carcinoma of the parotid gland with myoepithelial features. *Arch Pathol Lab Med* 2002; 126(9):1104-1105.
37. Henley JD, Rehan J, Oda D, et al. Metaplastic tumors of salivary gland origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 8: 197-188 (abstr).
38. Seifert G, Caselitz J. Tumor markers in parotid gland carcinomas: immunohistochemical investigations. *Cancer Detect Prev* 1983; 6(1-2):119-130.
39. Takahashi H, Fujita S, Okabe H, et al. Distribution of tissue markers in acinic cell carcinomas of salivary gland. *Pathol Res Pract* 1992; 188(6):692-700.
40. Caselitz J, Seifert G, Grenner G, et al. Amylase as an additional marker of salivary gland neoplasms. An immunoperoxidase study. *Pathol Res Pract* 1983; 176(2-4): 276-283.
41. Childers EL, Ellis GL, Auclair PL. An immunohistochemical analysis of anti-amylase antibody reactivity in acinic cell adenocarcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 81(6):691-694.
42. Hamper K, Schmitz-Wätjen W, Mausch HE, et al. Multiple expression of tissue markers in mucoepidermoid carcinomas and acinic cell carcinomas of the salivary glands. *Virchows Arch A Pathol Anat Histopathol* 1989; 414(5): 407-413.
43. Hayashi Y, Nishida T, Yoshida H, et al. Immunoreactive vasoactive intestinal polypeptide in acinic cell carcinoma of the parotid gland. *Cancer* 1987; 60(5):962-968.
44. Sakurai K, Urade M, Noguchi K, et al. Increased expression of cyclooxygenase-2 in human salivary gland tumors. *Pathol Int* 2001; 51(10):762-769.
45. Heikinheimo KA, Laine MA, Ritvos OV, et al. Bone morphogenetic protein-6 is a marker of serous acinar cell differentiation in normal and neoplastic human salivary gland. *Cancer Res* 1999; 59(22):5815-5821.
46. Jeannon JP, Soames JV, Bell H, et al. Immunohistochemical detection of oestrogen and progesterone receptors in salivary tumours. *Clin Otolaryngol Allied Sci* 1999; 24(1): 52-54.
47. Tazawa K, Kurihara Y, Kamoshida S, et al. Localization of prostate-specific antigen-like immunoreactivity in human salivary gland and salivary gland tumors. *Pathol Int* 1999; 49(6):500-505.
48. Prasad AR, Savera AT, Gown AM, et al. The myoepithelial immunophenotype in 135 benign and malignant salivary gland tumors other than pleomorphic adenoma. *Arch Pathol Lab Med* 1999; 123(9):801-806.
49. Bilal H, Handra-Luca A, Bertrand JC, et al. P63 is expressed in basal and myoepithelial cells of human normal and tumor salivary gland tissues. *J Histochem Cytochem* 2003; 51(2):133-139.
50. Gürbüz Y, Yildiz K, Aydin O, et al. Immunophenotypical profiles of salivary gland tumours: a new evidence for their histogenetic origin. *Pathologica* 2006; 98(2):147-152.
51. Gnepp DR, Brandwein MS, Henley JD. Salivary and lacrimal glands: acinic cell carcinoma. In: Gnepp DR, ed. *Diagnostic Surgical Pathology of the Head and Neck*. Philadelphia: WB Saunders, 2001:376-379.
52. Ihrler S, Blasenbren-Vogt S, Sendelhofert A, et al. Differential diagnosis of salivary acinic cell carcinoma and adenocarcinoma (NOS). A comparison of immuno-histochemical markers. *Pathol Res Pract* 2002; 198(12):777-783.
53. Sandros J, Mark J, Happonen RP, et al. Specificity of 6q- markers and other recurrent deviations in human malignant salivary gland tumors. *Anticancer Res* 1988; 8(4): 637-643.
54. Martins C, Fonseca I, Roque L, et al. Malignant salivary gland neoplasms: a cytogenetic study of 19 cases. *Eur J Cancer B Oral Oncol* 1996; 32B(2):128-132.
55. Jin C, Jin Y, Höglund M, et al. Cytogenetic and molecular genetic demonstration of polyclonality in an acinic cell carcinoma. *Br J Cancer* 1998; 78(3):292-295.
56. el-Naggar AK, Abdul-Karim FW, Hurr K, et al. Genetic alterations in acinic cell carcinoma of the parotid gland determined by microsatellite analysis. *Cancer Genet Cytogenet* 1998; 102(1):19-24.
57. Liu T, Zhu E, Wang L, et al. Abnormal expression of Rb pathway-related proteins in salivary gland acinic cell carcinoma. *Hum Pathol* 2005; 36(9):962-970.
58. Cerilli LA, Swartzbaugh JR, Saadut R, et al. Analysis of chromosome 9p21 deletion and p16 gene mutation in salivary gland carcinomas. *Hum Pathol* 1999; 30(10):1242-1246.
59. Lewis JE, Olsen KD, Weiland LH. Acinic cell carcinoma. Clinicopathologic review. *Cancer* 1991; 67(1):172-179.
60. Hickman RE, Cawson RA, Duffy SW. The prognosis of specific types of salivary gland tumors. *Cancer* 1984; 54(8):1620-1624.
61. Perzin KH, LiVolsi VA. Acinic cell carcinomas arising in salivary glands: a clinicopathologic study. *Cancer* 1979; 44(4):1434-1457.
62. Chen SY, Brannon RB, Miller AS, et al. Acinic cell adenocarcinoma of minor salivary glands. *Cancer* 1978; 42(2): 678-685.
63. Castellanos JL, Lally ET. Acinic cell tumor of the minor salivary glands. *J Oral Maxillofac Surg* 1982; 40(7):428-431.
64. Gardner DG, Bell ME, Wesley RK, et al. Acinic cell tumors of minor salivary glands. *Oral Surg Oral Med Oral Pathol* 1980; 50(6):545-551.

65. Zbaeren P, Lehmann W, Widgren S. Acinic cell carcinoma of minor salivary gland origin. *J Laryngol Otol* 1991; 105(9): 782–785.
66. Batsakis JG, Luna MA, el-Naggar AK. Histopathologic grading of salivary gland neoplasms: II. Acinic cell carcinomas. *Ann Otol Rhinol Laryngol* 1990; 99(11):929–933.
67. Timon CI, Dardick I, Panzarella T, et al. Clinico-pathological predictors of recurrence for acinic cell carcinoma. *Clin Otolaryngol Allied Sci* 1995; 20(5):396–401.
68. Skálová A, Leivo I, Boguslawsky K, et al. Cell proliferation correlates with prognosis in acinic cell carcinomas of salivary gland origin. Immunohistochemical study of 30 cases using the MIB 1 antibody in formalin-fixed paraffin sections. *J Pathol* 1994; 173(1):13–21.
69. Hellquist HB, Sundelin K, Di Bacco A, et al. Tumor growth fraction and apoptosis in salivary gland acinic cell carcinomas: prognostic implications of Ki-67 and bcl-2 expression and of in situ end labelling (TUNEL). *J Pathol* 1997; 181(3): 323–329.
70. Hamper K, Mausch HE, Caselitz J, et al. Acinic cell carcinoma of the salivary glands: the prognostic relevance of DNA cytophotometry in a retrospective study of long duration (1965–1987). *Oral Surg Oral Med Oral Pathol* 1990; 69(1):68–75.
71. el-Naggar AK, Batsakis JG, Luna MA, et al. DNA flow cytometry of acinic cell carcinomas of major salivary glands. *J Laryngol Otol* 1990; 104(5):410–416.
72. Gustafsson H, Lindholm C, Carlsöö B. DNA cytophotometry of acinic cell carcinoma and its relation to prognosis. *Acta Otolaryngol* 1987; 104(3–4):370–376.
73. Timon CI, Dardick I, Panzarella T, et al. Acinic cell carcinoma of salivary glands. Prognostic relevance of DNA flow cytometry and nucleolar organizer regions. *Arch Otolaryngol Head Neck Surg* 1994; 120(7):727–733.
11. Brookstone MS, Huvos AG. Central salivary gland tumors of the maxilla and mandible: a clinicopathologic study of 11 cases with an analysis of the literature. *J Oral Maxillofac Surg* 1992; 50(3):229–236.
12. Martínez-Madrigal F, Pineda-Daboin K, Casiraghi O, et al. Salivary gland tumors of the mandible. *Ann Diagn Pathol* 2000; 4(6):347–353.
13. Pires FR, Chen SY, da Cruz Perez DE, et al. Cytokeratin expression in central mucoepidermoid carcinoma and glandular odontogenic cyst. *Oral Oncol* 2004; 40(5): 545–551.
14. Nagao K, Matsuzaki O, Saiga H, et al. Histopathological studies on parotid gland tumors in Japanese children. *Virchows Arch A Pathol Anat Histol* 1980; 388(3): 263–272.
15. Guzzo M, Ferrari A, Marcon I, et al. Salivary gland neoplasms in children: the experience of the Istituto Nazionale Tumori di Milan. *Pediatr Blood Cancer* 2006; 47(6):806–810.
16. Saku T, Hayashi Y, Takahara O, et al. Salivary gland tumors among atomic bomb survivors, 1950–1987. *Cancer* 1997; 79(8):1465–1475.
17. Whatley WS, Thompson JW, Rao B. Salivary gland tumors in survivors of childhood cancer. *Otolaryngol Head Neck Surg* 2006; 134(3):385–388.
18. Ogawa I, Nikai H, Takata T, et al. Clear-cell variant of mucoepidermoid carcinoma: report of a case with immunohistochemical and ultrastructural observations. *J Oral Maxillofac Surg* 1992; 50(8):906–910.
19. Ellis GL. Clear cell neoplasms in salivary glands: clearly a diagnostic challenge. *Ann Diagn Pathol* 1998; 2(1):61–78.
20. Brannon RB, Willard CC. Oncocytic mucoepidermoid carcinoma of parotid gland origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(6):727–733.
21. Corcione L, Giordano G, Gnetti L, et al. Oncocytic mucoepidermoid carcinoma of a submandibular gland: a case report and review of the literature. *Int J Oral Maxillofac Surg* 2007; 36(6):560–563.
22. Takeda Y, Kurose A. Pigmented mucoepidermoid carcinoma, a case report and review of the literature on melanin-pigmented salivary gland tumors. *J Oral Sci* 2006; 48(4):253–256.
23. Chan JK, Saw D. Sclerosing mucoepidermoid tumour of the parotid gland: report of a case. *Histopathology* 1987; 11(2):203–207.
24. Urano M, Abe M, Horibe Y, et al. Sclerosing mucoepidermoid carcinoma with eosinophilia of the salivary glands. *Pathol Res Pract* 2002; 198(4):305–310.
25. Veras EF, Sturgis E, Luna MA. Sclerosing mucoepidermoid carcinoma of the salivary glands. *Ann Diagn Pathol* 2007; 11(6):407–412.
26. Auclair PL. Tumor-associated lymphoid proliferation in the parotid gland. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):19–26.
27. Healey WV, Perzin KH, Smith L. Mucoepidermoid carcinoma of salivary gland origin: classification, clinical-pathologic correlation, and results of treatment. *Cancer* 1970; 26(2):368–388.
28. Batsakis JG, Luna MA. Histopathologic grading of salivary gland neoplasms: I. Mucoepidermoid carcinomas. *Ann Otol Rhinol Laryngol* 1990; 99(10 pt1):835–838.
29. Auclair PL, Goode RK, Ellis GL. Mucoepidermoid carcinoma of intraoral salivary glands: evaluation and application of grading criteria in 143 cases. *Cancer* 1992; 69(8): 2021–2030.
30. Hicks MJ, El-Naggar AK, Flaitz CM, et al. Histocytologic grading of mucoepidermoid carcinoma of major salivary literature and discussion of the relationship to mucoepidermoid, sialodontogenic, and glandular odontogenic cysts. *J Oral Maxillofac Surg* 1990; 48(8):871–877.

Mucoepidermoid Carcinoma

1. Ellis GL, Auclair PL. Mucoepidermoid carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:155–175.
2. Goode RK, El-Naggar AK. Mucoepidermoid carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:219–220.
3. Stewart FW, Foote FW, Becker WF. Mucoepidermoid tumors of salivary glands. *Ann Surg* 1945; 122(5):820–844.
4. Foote FW, Frazell EI. Tumors of the major salivary glands. *Cancer* 1953; 6(6):1065–1133.
5. Thackray AC, Sobin LH. *World Health Organization International Histological Classification of Tumours: Histological Typing of Salivary Gland Tumours*. Berlin: Springer-Verlag, 1972.
6. Seifert G, Sobin LH. *World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours*. 2nd ed. Berlin: Springer-Verlag, 1991.
7. Spiro RH, Huvos AG, Berk R, et al. Mucoepidermoid carcinoma of salivary gland origin: a clinicopathologic study of 367 cases. *Am J Surg* 1978; 136(4):461–468.
8. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol* 1985; 146(1):51–58.
9. Daniel E, McGuirt WF Sr. Neck masses secondary to heterotopic salivary gland tissue: a 25-year experience. *Am J Otolaryngol* 2005; 26(2):96–100.
10. Waldron CA, Koh ML. Central mucoepidermoid carcinoma of the jaws: report of four cases with analysis of the

- glands in prognosis and survival: a clinicopathologic and flow cytometric investigation. *Head Neck* 1995; 17(2):89–95.
31. Goode RK, Auclair PL, Ellis GL. Mucoepidermoid carcinoma of the major salivary glands: clinical and histopathologic analysis of 234 cases with evaluation of grading criteria. *Cancer* 1998; 82(7):1217–1224.
 32. Brandwein MS, Ivanov K, Wallace DI, et al. Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histologic grading. *Am J Surg Pathol* 2001; 25(7):835–845.
 33. Luna MA. Salivary mucoepidermoid carcinoma: revisited. *Adv Anat Pathol* 2006; 13(6):293–307.
 34. Guzzo M, Andreola S, Sirizzotti G, et al. Mucoepidermoid carcinoma of the salivary glands: clinicopathologic review of 108 patients treated at the National Cancer Institute of Milan. *Ann Surg Oncol* 2002; 9(7):688–695.
 35. Nagao T, Gaffey TA, Kay PA, et al. Dedifferentiation in low-grade mucoepidermoid carcinoma of the parotid gland. *Hum Pathol* 2003; 34(10):1068–1072.
 36. Love GL, Sarma DP. Spindle cell mucoepidermoid carcinoma of submandibular gland. *J Surg Oncol* 1986; 31(1):66–68.
 37. Nagao T, Sugano I, Ishida Y, et al. Mucoepidermoid carcinoma arising in Warthin's tumour of the parotid gland: report of two cases with histopathological, ultrastructural and immunohistochemical studies. *Histopathology* 1998; 33(4):379–386.
 38. Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: pathologic analysis of 73 cases. *Hum Pathol* 2001; 32(6):596–604.
 39. Seifert G. Mucoepidermoid carcinoma in a salivary duct cyst of the parotid gland. Contribution to the development of tumours in salivary gland cysts. *Pathol Res Pract* 1996; 192(12):1211–1217.
 40. Rizkalla H, Toner M. Necrotizing sialometaplasia versus invasive carcinoma of the head and neck: the use of myoepithelial markers and keratin subtypes as an adjunct to diagnosis. *Histopathology* 2007; 51(2):184–189.
 41. El-Naggar AK, Lovell M, Killary AM, et al. A mucoepidermoid carcinoma of minor salivary gland with t(11;19)(q21;p13.1) as the only karyotypic abnormality. *Cancer Genet Cytogenet* 1996; 87(1):29–33.
 42. Behboudi A, Enlund F, Winnes M, et al. Molecular classification of mucoepidermoid carcinomas-prognostic significance of the MECT1-MAML2 fusion oncogene. *Genes Chromosomes Cancer* 2006; 45(5):470–481.
 43. Okabe M, Miyabe S, Nagatsuka H, et al. MECT1-MAML2 fusion transcript defines a favorable subset of mucoepidermoid carcinoma. *Clin Cancer Res* 2006; 12(13):3902–3907.
 44. Tirado Y, Williams MD, Hanna EY, et al. CRTC1/MAML2 fusion transcript in high grade mucoepidermoid carcinomas of salivary and thyroid glands and Warthin's tumors: implications for histogenesis and biologic behavior. *Genes Chromosomes Cancer* 2007; 46(7):708–715.
 45. Tonon G, Modi S, Wu L, et al. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. *Nat Genet* 2003; 33(2):208–213.
 46. Möller E, Stenman G, Mandahl N, et al. POU5F1, encoding a key regulator of stem cell pluripotency, is fused to EWSR1 in hidradenoma of the skin and mucoepidermoid carcinoma of the salivary glands. *J Pathol* 2008; 215(1):78–86.
 47. Kaye FJ. Emerging biology of malignant salivary gland tumors offers new insights into the classification and treatment of mucoepidermoid cancer. *Clin Cancer Res* 2006; 12(13):3878–3881.
 48. Handra-Luca A, Lamas G, Bertrand JC, et al. MUC1, MUC2, MUC4, and MUC5AC expression in salivary gland mucoepidermoid carcinoma: diagnostic and prognostic implications. *Am J Surg Pathol* 2005; 29(7):881–889.
 49. Alos L, Lujan B, Castillo M, et al. Expression of membrane-bound mucins (MUC1 and MUC4) and secreted mucins (MUC2, MUC5AC, MUC5B, MUC6 and MUC7) in mucoepidermoid carcinomas of salivary glands. *Am J Surg Pathol* 2005; 29(6):806–813.
 50. Nikitakis NG, Tosios KI, Papanikolaou VS, et al. Immunohistochemical expression of cytokeratins 7 and 20 in malignant salivary gland tumors. *Mod Pathol* 2004; 17(4):407–415.
 51. Maiorano E, Altini M, Favia G. Clear cell tumors of the salivary glands, jaws and oral mucosa. *Semin Diagn Pathol* 1997; 14(3):203–212.
 52. Hicks MJ, El-Naggar AK, Byers RM, et al. Prognostic factors in mucoepidermoid carcinomas of major salivary glands: a clinicopathologic and flow cytometric study. *Eur J Cancer B Oral Oncol* 1994; 30B(5):329–334.
 53. Skalova A, Lehtonen H, von Boguslawsky K, et al. Prognostic significance of cell proliferation in mucoepidermoid carcinomas of the salivary gland: clinicopathological study using MIB 1 antibody in paraffin sections. *Hum Pathol* 1994; 25(9):929–935.
 54. Okabe M, Inagaki H, Murase T, et al. Prognostic significance of p27 and Ki-67 expression in mucoepidermoid carcinoma of the intraoral minor salivary gland. *Mod Pathol* 2001; 14(10):1008–1014.
 55. Nguyen LH, Black MJ, Hier M, et al. HER2/neu and Ki-67 as prognostic indicators in mucoepidermoid carcinoma. *J Otolaryngol* 2003; 32(5):328–331.
 56. Pires FR, de Almeida OP, de Araújo VC, et al. Prognostic factors in head and neck mucoepidermoid carcinoma. *Arch Otolaryngol Head Neck Surg* 2004; 130(2):174–180.
 57. Yin HF, Okada N, Takagi M. Apoptosis and apoptotic-related factors in mucoepidermoid carcinoma of the oral minor salivary glands. *Pathol Int* 2000; 50(8):603–609.
 58. Shi L, Chen XM, Wang L, et al. Expression of caveolin-1 in mucoepidermoid carcinoma of the salivary glands: correlation with vascular endothelial growth factor, microvessel density, and clinical outcome. *Cancer* 2007; 109(8):1523–1531.
 59. Shiratsuchi H, Nakashima T, Hirakawa N, et al. β -Catenin nuclear accumulation in head and neck mucoepidermoid carcinoma: its role in cyclin D1 overexpression and tumor progression. *Head Neck* 2007; 29(6):577–584.

Adenoid Cystic Carcinoma

1. El-Naggar AK, Huvos AG. Adenoid cystic carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:221–222.
2. Ellis GL, Auclair PL, Gnepp DR, et al. Salivary gland neoplasms: general considerations. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:144–145.
3. Tomich CE. Adenoid cystic carcinoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:333–349.
4. Jones DC, Bainton R. Adenoid cystic carcinoma of the palate in a 9-year-old boy. *Oral Surg Oral Med Oral Pathol* 1990; 69(4):483–486.
5. Ellis GL, Auclair PL. Adenoid cystic carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:203–216.
6. Matsuba HM, Thawley SE, Simpson JR, et al. Adenoid cystic carcinoma of major and minor salivary gland origin. *Laryngoscope* 1984; 94(10):1316–1318.

7. Nascimento AG, Amaral AL, Prado LA, et al. Adenoid cystic carcinoma of salivary glands. A study of 61 cases with clinicopathologic correlation. *Cancer* 1986; 57(2):312-319.
8. Perzin KH, Gullane P, Clairmont AC. Adenoid cystic carcinomas arising in salivary glands: a correlation of histologic features and clinical course. *Cancer* 1978; 42(1): 265-282.
9. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. *Am J Surg* 1974; 128(4):512-520.
10. Cohen AN, Damrose EJ, Huang RY, et al. Adenoid cystic carcinoma of the submandibular gland: a 35-year review. *Otolaryngol Head Neck Surg* 2004; 131(6):994-1000.
11. Gnepp DR, Brandwein MS, Henley JD. Salivary and lacrimal glands. In: Gnepp DR, eds. *Diagnostic Surgical Pathology of the Head and Neck*. Philadelphia: WB Saunders, 2000:380.
12. Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. *Am J Surg* 1992; 164(6):623-628.
13. Conley J, Caster JD. *Adenoid Cystic Cancer of the Head and Neck*. New York: Thieme Medical Publishers, 1991.
14. Garden AS, Weber RS, Morrison WH, et al. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995; 32(3):619-626.
15. Kim KH, Sung MW, Chung PS, et al. Adenoid cystic carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1994; 120(7):721-726.
16. Yu T, Gao QH, Wang XY, et al. Malignant sublingual gland tumors: a retrospective clinicopathologic study of 28 cases. *Oncology* 2007; 72(1-2):39-44.
17. Spiro RH, Koss LG, Hajdu SI, et al. Tumors of minor salivary origin. A clinicopathologic study of 492 cases. *Cancer* 1973; 31(1):117-129.
18. Lupinetti AD, Roberts DB, Williams MD, et al. Sinonasal adenoid cystic carcinoma: the M.D. Anderson Cancer Center experience. *Cancer* 2007; 110(12):2726-2731.
19. Al-Sukhun J, Lindqvist C, Hietanen J, et al. Central adenoid cystic carcinoma of the mandible: case report and literature review of 16 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 101(3):304-308.
20. Friedrich RE, Bleckmann V. Adenoid cystic carcinoma of salivary and lacrimal gland origin: localization, classification, clinical pathological correlation, treatment results and long-term follow-up control in 84 patients. *Anticancer Res* 2003; 23(2A):931-940.
21. Garbyal RS, Kumar M, Bohra A. Adenoid cystic carcinoma of ceruminous gland: a case report. *Indian J Pathol Microbiol* 2006; 49(4):587-589.
22. Karaoglanoglu N, Eroglu A, Turkyilmaz A, et al. Oesophageal adenoid cystic carcinoma and its management options. *Int J Clin Pract* 2005; 59(9):1101-1103.
23. Hajdu SI, Huvos AG, Goodner JT, et al. Carcinoma of the trachea. Clinicopathologic study of 41 cases. *Cancer* 1970; 25(6):1448-1456.
24. Azukari K, Yoshioka K, Seto S, et al. Adenoid cystic carcinoma arising in the intrapulmonary bronchus. *Intern Med* 1996; 35(5):407-409.
25. Yokouchi H, Otsuka Y, Otoguro Y, et al. Primary peripheral adenoid cystic carcinoma of the lung and literature comparison of features. *Intern Med* 2007; 46(21):1799-1803.
26. Muslimani AA, Ahluwalia MS, Clark CT, et al. Primary adenoid cystic carcinoma of the breast: case report and review of the literature. *Int Semin Surg Oncol* 2006; 3:17.
27. Urso C, Bondi R, Paglierani M, et al. Carcinomas of sweat glands: report of 60 cases. *Arch Pathol Lab Med* 2001; 125(4):498-505.
28. Koyfman SA, Abidi A, Ravichandran P, et al. Adenoid cystic carcinoma of the cervix. *Gynecol Oncol* 2005; 99(2): 477-480.
29. Zámecník M, Michal M, Curík R. Adenoid cystic carcinoma of the ovary. *Arch Pathol Lab Med* 2000; 124(10):1529-1531.
30. Woida FM, Ribeiro-Silva A. Adenoid cystic carcinoma of the Bartholin gland: an overview. *Arch Pathol Lab Med* 2007; 131(5):796-798.
31. Begnami MD, Quezado M, Pinto P, et al. Adenoid cystic/basal cell carcinoma of the prostate: review and update. *Arch Pathol Lab Med* 2007; 131(4):637-640.
32. Warren CJ, Gnepp DR, Rosenblum BN. Adenoid cystic carcinoma metastasizing before detection of the primary lesion. *South Med J* 1989; 82(10):1277-1279.
33. Wal van der JE, Snow GB, Karim AB, et al. Adenoid cystic carcinoma of the palate with squamous metaplasia or basaloid-squamous carcinoma? Report of a case. *J Oral Pathol Med* 1994; 23(10):461-464.
34. Cramer SF, Gnepp DR, Kiehn CL, et al. Sebaceous differentiation in adenoid cystic carcinoma of the parotid gland. *Cancer* 1980; 46(6):1405-1410.
35. Moles MA, Avila IR, Archilla AR. Dedifferentiation occurring in adenoid cystic carcinoma of the tongue. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 88(2): 177-180.
36. Cheuk W, Chan JK, Ngan RK. Dedifferentiation in adenoid cystic carcinoma of salivary gland: an uncommon complication associated with an accelerated clinical course. *Am J Surg Pathol* 1999; 23(4):465-472.
37. Chau Y, Hongyo T, Aozasa K, et al. Dedifferentiation of adenoid cystic carcinoma: report of a case implicating p53 gene mutation. *Hum Pathol* 2001; 32(12):1403-1407.
38. Nagao T, Gaffey TA, Serizawa H, et al. Dedifferentiated adenoid cystic carcinoma: a clinicopathologic study of 6 cases. *Mod Pathol* 2003; 16(12):1265-1272.
39. Seethala RR, Hunt JL, Baloch ZW, et al. Adenoid cystic carcinoma with high-grade transformation: a report of 11 cases and a review of the literature. *Am J Surg Pathol* 2007; 31(11):1683-1694.
40. Nagao T, Sugano I, Ishida Y, et al. Hybrid carcinomas of the salivary glands: report of nine cases with a clinicopathologic, immunohistochemical, and p53 gene alteration analysis. *Mod Pathol* 2002; 15(7):724-733.
41. Azzopardi JG, Zayid I. Elastic tissue in tumours of salivary glands. *J Pathol* 1972; 107(3):149-156.
42. Adkins KF, Daley TJ. Elastic tissue in adenoid cystic carcinomas. *Oral Surg Oral Med Oral Pathol* 1974; 38(4):562-569.
43. Albores-Saavedra J, Wu J, Uribe-Uribe N. The sclerosing variant of adenoid cystic carcinoma: a previously unrecognized neoplasm of major salivary glands. *Ann Diagn Pathol* 2006; 10(1):1-7.
44. Allen MS Jr., Marsh WL Jr. Lymph node involvement by direct extension in adenoid cystic carcinoma. Absence of classic embolic lymph node metastasis. *Cancer* 1976; 38(5):2017-2021.
45. Cheng J, Saku T, Okabe H, et al. Basement membranes in adenoid cystic carcinoma. An immunohistological study. *Cancer* 1992; 69(11):2631-2640.
46. Kumamoto M, Kuratomi Y, Yasumatsu R, et al. Expression of laminin 5 basement membrane components in invading and recurring adenoid cystic carcinoma of the head and neck. *Auris Nasus Larynx* 2006; 33(2):167-172.
47. Chen JC, Gnepp DR, Bedrossian CW. Adenoid cystic carcinoma of the salivary glands: an immunohistochemical analysis. *Oral Surg Oral Med Oral Pathol* 1988; 65(3):316-326.
48. Jeng YM, Lin CY, Hsu HC. Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma. *Cancer Lett* 2000; 154(1):107-111.
49. Edwards PC, Bhuiya T, Kelsch RD. C-kit expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and monomorphic

- adenoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 95(5):586–593.
50. Mino M, Pilch BZ, Faquin WC. Expression of KIT (CD117) in neoplasms of the head and neck: an ancillary marker for adenoid cystic carcinoma. *Mod Pathol* 2003; 16(12):1224–1231.
51. Emanuel P, Wang B, Wu M, et al. p63 Immunohistochemistry in the distinction of adenoid cystic carcinoma from basaloid squamous cell carcinoma. *Mod Pathol* 2005; 18(5):645–650.
52. Prasad AR, Saveria AT, Gown AM, et al. The myoepithelial immunophenotype in 135 benign and malignant salivary gland tumors other than pleomorphic adenoma. *Arch Pathol Lab Med* 1999; 123(9):801–806.
53. Prasad ML, Barbacioru CC, Rawal YB, et al. Hierarchical cluster analysis of myoepithelial/basal cell markers in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. *Mod Pathol* 2008; 21(2):105–114.
54. Luo X-L, Sun M-Y, Lu C-T, et al. The role of Schwann cell differentiation in perineural invasion of adenoid cystic and mucoepidermoid carcinoma of the salivary gland. *Int J Oral Maxillofac Surg* 2006; 35(8):733–739.
55. Shang J, Sheng L, Wang K, et al. Expression of neural cell adhesion molecule in salivary adenoid cystic carcinoma and its correlation with perineural invasion. *Oncol Rep* 2007; 18(6):1413–1416.
56. Yamamoto Y, Wistuba II, Kishimoto Y, et al. DNA analysis at p53 locus in adenoid cystic carcinoma: comparison of molecular study and p53 immunostaining. *Pathol Int* 1998; 48(4):273–280.
57. Carlinfante G, Lazzaretti M, Ferrari S, et al. p53, bcl-2 and Ki-67 expression in adenoid cystic carcinoma of the palate. A clinico-pathologic study of 21 cases with long-term follow-up. *Pathol Res Pract* 2005; 200(11–12):791–799.
58. da Cruz Perez DE, de Abreu Alves F, Nobuko Nishimoto I, et al. Prognostic factors in head and neck carcinoma. *Oral Oncol* 2006; 42(2):139–146.
59. Woo VL, Bhuiya T, Kelsch R. Assessment of CD43 expression in adenoid cystic carcinomas, polymorphous low-grade carcinomas, and monomorphic adenomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endo* 2006; 102(4):495–500.
60. Seethala RR, Pasha TL, Raghunath PN, et al. The selective expression of CD43 in adenoid cystic carcinoma. *Appl Immunohistochem Mol Morphol* 2008; 16(2):165–172.
61. Sandros J, Mark J, Happonen RP, et al. Specificity of 6q-markers and other recurrent deviations in human malignant salivary gland tumors. *Anticancer Res* 1988; 8(4):637–643.
62. Jin C, Martins C, Jin Y, et al. Characterization of chromosome aberrations in salivary gland tumors by FISH, including multicolor COBRA-FISH. *Genes Chromosomes Cancer* 2001; 30(2):161–167.
63. Nordkvist A, Mark J, Gustafsson H, et al. Non-random chromosome rearrangements in adenoid cystic carcinoma of the salivary glands. *Genes Chromosomes Cancer* 1994; 10(2):115–121.
64. El-Rifai W, Rutherford S, Knuutila S, et al. Novel DNA copy number losses in chromosome 12q12–q13 in adenoid cystic carcinoma. *Neoplasia* 2001; 3(3):173–178.
65. Stallmach I, Zenklusen P, Komminoth P, et al. Loss of heterozygosity at chromosome 6q23–25 correlates with clinical and histologic parameters in salivary gland adenoid cystic carcinoma. *Virchows Arch* 2002; 440(1):77–84.
66. Queimado L, Reis A, Fonseca I, et al. A refined localization of two deleted regions in chromosome 6q associated with salivary gland carcinomas. *Oncogene* 1998; 16(1):83–88.
67. Rutherford S, Yu Y, Rumpel CA, et al. Chromosome 6 deletion and candidate tumor suppressor genes in adenoid cystic carcinoma. *Cancer Lett* 2006; 236(2):309–317.
68. Rutherford S, Hampton GM, Frierson HF, et al. Mapping of candidate tumor suppressor genes on chromosome 12 in adenoid cystic carcinoma. *Lab Invest* 2005; 85(9):1076–1085.
69. Maruya S, Kurotaki H, Shimoyama N, et al. Expression of p16 protein and hypermethylation status of its promoter gene in adenoid cystic carcinoma of the head and neck. *ORL J Otorhinolaryngol Relat Spec* 2003; 65(1):26–32.
70. Li J, El-Naggar A, Mao L. Promoter methylation of p16INK4a, RASSF1A, and DAPK is frequent in salivary adenoid cystic carcinoma. *Cancer* 2005; 104(4):771–776.
71. Papadakis H, Finkelstein SD, Kounelis S, et al. The role of p53 mutation and protein expression in primary and recurrent adenoid cystic carcinoma. *Hum Pathol* 1996; 27(6):567–572.
72. Kiyoshima T, Shima K, Kobayashi I, et al. Expression of p53 tumor suppressor gene in adenoid cystic and mucoepidermoid carcinomas of salivary glands. *Oral Oncol* 2001; 27(3):315–322.
73. Yamamoto Y, Virmani AK, Wistuba II, et al. Loss of heterozygosity and microsatellite alterations in p53 and RB genes in adenoid cystic carcinomas of the salivary glands. *Hum Pathol* 1996; 27(11):1204–1210.
74. Daa T, Kashima K, Kondo Y, et al. Aberrant methylation in promoter regions of cyclin-dependent kinase inhibitor genes in adenoid cystic carcinoma of the salivary gland. *APMIS* 2008; 116(1):21–26.
75. Kamsamatsu A, Endo Y, Uzawa K, et al. Identification of candidate genes associated with salivary adenoid cystic carcinomas using combined comparative genomic hybridization and oligonucleotide microarray analyses. *Int J Biochem Cell Biol* 2005; 37(9):1869–1880.
76. Castle JT, Thompson LD, Frommelt RA, et al. Polymorphous low grade adenocarcinoma: a clinicopathologic study of 164 cases. *Cancer* 1999; 86(2):207–219.
77. Gnepp DR, Chen JC, Warren C. Polymorphous low-grade adenocarcinoma of minor salivary gland. An immunohistochemical and clinicopathologic study. *Am J Surg Pathol* 1988; 12(6):461–468.
78. Skalova A, Simpson RH, Lehtonen H, et al. Assessment of proliferative activity using the MIB1 antibody help to distinguish polymorphous low grade adenocarcinoma from adenoid cystic carcinoma of salivary glands. *Pathol Res Pract* 1997; 193(10):695–703.
79. Aslan DL, Oprea GM, Jagush SM, et al. c-kit expression in adenoid cystic carcinoma does not have an impact on local or distant tumor recurrence. *Head Neck* 2005; 27(12):1028–1034.
80. Ogawa I, Miyauchi M, Matsuura H, et al. Pleomorphic adenoma with extensive adenoid cystic carcinoma-like cribriform areas of parotid gland. *Pathol Int* 2003; 53(1):30–34.
81. Spiro R. The controversial adenoid cystic carcinoma. Is this cancer curable and where does it fail? The nature of adenoid cystic carcinoma. In: McGurk M, Renehan A, eds. *Controversies in The Management of Salivary Gland Disease*. Oxford: Oxford University Press, 2002:207–211.
82. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma: factors influencing survival. *Am J Surg* 1979; 138(4):579–583.
83. Szanto PA, Luna MA, Tortoledo ME, et al. Histologic grading of adenoid cystic carcinoma of the salivary glands. *Cancer* 1984; 54(6):1062–1069.
84. Batsakis JG, Luna MA, el-Naggar A. Histopathologic grading of salivary gland neoplasms: III. Adenoid cystic carcinomas. *Ann Otol Rhinol Laryngol* 1990; 99(12):1007–1009.
85. Fordice J, Kershaw C, El-Naggar A, et al. Adenoid cystic carcinoma of the head and neck: predictors of morbidity and mortality. *Arch Otolaryngol Head Neck Surg* 1999; 125(2):149–152.

86. Jones AS, Hamilton JW, Rowley H, et al. Adenoid cystic carcinoma of the head and neck. *Clin Otolaryngol Allied Sci* 1997; 22(5):434-443.
87. Luna MA, el-Naggar A, Batsakis JG, et al. Flow cytometric DNA content of adenoid cystic carcinoma of submandibular gland. Correlation of histologic features and prognosis. *Arch Otolaryngol Head Neck Surg* 1990; 116(11):1291-1296.
88. Franzén G, Klausén OG, Grenko RT, et al. Adenoid cystic carcinoma: DNA as a prognostic indicator. *Laryngoscope* 1991; 101(6 pt 1):669-673.
89. Tytor M, Gemryd P, Grenko R, et al. Adenoid cystic carcinoma: significance of DNA ploidy. *Head Neck* 1995; 17(4):319-327.
90. Nordgård S, Franzén G, Boysen M, et al. Ki-67 as a prognostic marker in adenoid cystic carcinoma assessed with the monoclonal antibody MIB1 in paraffin sections. *Laryngoscope* 1997; 107(4):531-536.
91. Barrett A, Speight P. The controversial adenoid cystic carcinoma. The implications of histological grade and perineural invasion. In: McGurk M, Renehan A, eds. *Controversies in The Management of Salivary Gland Disease*. Oxford: Oxford University Press, 2002:211-217.
92. Spiro RH. Distant metastasis in adenoid cystic carcinoma of salivary origin. *Am J Surg* 1997; 174(5):495-498.
93. Gurney TA, Eisele DW, Weinberg V, et al. Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation. *Laryngoscope* 2005; 115(7):1278-1282.
94. Gomez DR, Hoppe BS, Wolden SL, et al. Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. *Int J Radiat Oncol Biol Phys* 2008; 70(5):1365-1372.
95. Hotte SJ, Winquist EW, Lamont E, et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. *J Clin Oncol* 2005; 23(3):585-590.
96. Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol* 2007; 25(25): 3978-3984.
8. Michal M, Skálová A, Simpson RHW, et al. Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue. *Histopathology* 1999; 35(6):495-501.
9. Aberle AM, Abrams AM, Bowe R, et al. Lobular (polymorphous low-grade) carcinoma of minor salivary glands: a clinicopathologic study of twenty cases. *Oral Surg Oral Med Oral Pathol* 1985; 60(4):387-395.
10. Vincent SD, Hammond HL, Finkelstein MW. Clinical and therapeutic features of polymorphous low-grade adenocarcinoma. *Oral Surg Oral Med Oral Pathol* 1994; 77(1): 41-47.
11. Perez-Ordóñez B, Linkov L, Huvos AG. Polymorphous low-grade adenocarcinoma of minor salivary glands: a study of 17 cases with emphasis on cell differentiation. *Histopathology* 1998; 32(11):521-529.
12. Castle JT, Thompson LDR, Frommelt RA, et al. Polymorphous low-grade adenocarcinoma: a clinicopathologic study of 164 cases. *Cancer* 1999; 86(2):207-219.
13. Evans HL, Luna MA. Polymorphous low-grade adenocarcinoma: a study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas. *Am J Surg Pathol* 2000; 24(10):1319-1328.
14. Paleri V, Robinson M, Bradley P. Polymorphous low-grade adenocarcinoma of the head and neck. *Curr Opin Otolaryngol Head Neck Surg* 2008; 16(2):163-169.
15. Selva D, Davis GJ, Dodd T, et al. Polymorphous low-grade adenocarcinoma of the lacrimal gland. *Arch Ophthalmol* 2004; 122(6):915-917.
16. Wenig BM, Harpaz N, DelBridge C. Polymorphous low-grade adenocarcinoma of seromucous glands of the nasopharynx: a report of a case and a discussion of the morphologic and immunohistochemical features. *Am J Clin Pathol* 1989; 92(1):104-109.
17. Toida M, Shimokawa K, Makita H, et al. Intraoral minor salivary gland tumors: a clinicopathological study of 82 cases. *Int J Oral Maxillofac Surg* 2005; 34(5):528-532.
18. Clayton JR, Pogrel A, Regezi JA. Simultaneous multifocal polymorphous low-grade adenocarcinoma: report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 80(1):71-77.
19. Tortoledo ME, Luna MA, Batsakis JG. Carcinomas ex pleomorphic adenoma and malignant mixed tumors: histomorphologic indexes. *Arch Otolaryngol* 1984; 110(3): 172-176.
20. Foss R, Ellis G, Auclair P. Salivary gland cystadenocarcinomas: a clinicopathologic study of 57 cases. *Am J Surg Pathol* 1996; 20(12):1440-1447.
21. Raubenheimer EJ, van Heerden WF, Thein T. Tyrosine-rich crystalloids in a polymorphous low-grade adenocarcinoma. *Oral Surg Oral Med Oral Pathol* 1990; 70(4):480-482.
22. Pelkey TJ, Mills SE. Histologic transformation of polymorphous low-grade adenocarcinoma of salivary gland. *Am J Clin Pathol* 1999; 111(6):785-791.
23. Simpson RHW, Reis-Filho JS, Pereira EM, et al. Polymorphous low-grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. *Histopathology* 2002; 41(3):250-259.
24. Gnepp DR, El-Mofty S. Polymorphous low-grade adenocarcinoma: glial fibrillary acidic protein staining in the differential diagnosis with cellular mixed tumors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 83(6):691-695.
25. Araújo V, Sousa S, Jaeger M, et al. Characterization of the cellular component of polymorphous low-grade adenocarcinoma by immunohistochemistry and electron microscopy. *Oral Oncol* 1999; 35(2):164-172.
26. Curran AE, White DK, Damm DD, et al. Polymorphous low-grade adenocarcinoma versus pleomorphic adenoma

Polymorphous Low-Grade Adenocarcinoma

1. Evans HL, Batsakis JG. Polymorphous low-grade adenocarcinoma of minor salivary glands: a study of 14 cases of a distinctive neoplasm. *Cancer* 1984; 53(4):935-942.
2. Batsakis JG, Pinkston GR, Luna MA, et al. Adenocarcinomas of the oral cavity: a clinicopathologic study of terminal duct adenocarcinomas. *J Laryngol Otol* 1983; 97(9):825-835.
3. Freedman PD, Lummerman H. Lobular carcinoma of intraoral minor salivary gland origin. *Oral Surg Oral Med Oral Pathol* 1983; 56(2):157-165.
4. Luna MA, Wenig BM. Polymorphous low-grade adenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:223-224.
5. Ellis GL, Auclair PL. Polymorphous low-grade adenocarcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:216-228.
6. Waldron CA, El-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* 1988; 66(3):323-333.
7. Nagao T, Gaffey TA, Kay PA, et al. Polymorphous low-grade adenocarcinoma of the major salivary glands: report of three cases in an unusual location. *Histopathology* 2004; 44(2):164-171.

- of minor salivary glands: resolution of a diagnostic dilemma by immunohistochemical analysis with glial acidic protein. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 91(2):194–199.
27. Prasad ML, Barbacioru CC, Rawal YB, et al. Hierarchical cluster analysis of myoepithelial/basal cell markers in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. *Mod Pathol* 2008; 21(2):105–114.
 28. Skálová A, Simpson RH, Lehtonen H, et al. Assessment of proliferation activity using the MIB1 antibody help to distinguish polymorphous low-grade adenocarcinoma from adenoid cystic carcinoma of salivary glands. *Pathol Res Pract* 1997; 193(10):695–703.
 29. Penner CR, Folpe AL, Budnick SD. C-kit expression distinguishes salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma. *Mod Pathol* 2002; 15(7):687–691.
 30. Edwards PC, Bhuiya T, Kelsch RD. C-kit expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and monomorphic adenoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 95(5):586–593.
 31. Slootweg PJ. Low-grade adenocarcinoma of the oral cavity: polymorphous or papillary? *J Oral Pathol Med* 1993; 22(7):327–330.
 13. Fonseca I, Soares J. Epithelial-myoepithelial carcinoma of the salivary glands. A study of 22 cases. *Virchows Arch A Pathol Anat Histopathol* 1993; 422(5):389–396.
 14. Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. *Am J Surg Pathol* 2007; 31(1):44–57.
 15. Morinaga S, Hashimoto S, Tezuka F. Epithelial-myoepithelial carcinoma of the parotid gland in a child. *Acta Pathol Jpn* 1992; 42(5):358–363.
 16. Horinouchi H, Ishihara T, Kawamura M, et al. Epithelial myoepithelial tumour of the tracheal gland. *J Clin Pathol* 1993; 46(2):185–187.
 17. Imate Y, Yamashita H, Endo S, et al. Epithelial-myoepithelial carcinoma of the nasopharynx. *ORL J Otorhinolaryngol Relat Spec* 2000; 62(5):282–285.
 18. Pelosi G, Frassetto F. Epithelial-myoepithelial carcinomas of the bronchus. *Am J Surg Pathol* 2002; 26(7):950–951.
 19. Doganay L, Bilgi S, Ozdil A, et al. Epithelial-myoepithelial carcinoma of the lung. A case report and review of the literature. *Arch Pathol Lab Med* 2003; 127(4):177–180.
 20. Seifert G. Are adenomyoepithelioma of the breast and epithelial-myoepithelial carcinoma of the salivary glands identical tumours? *Virchows Arch* 1998; 433(3):285–288.
 21. Shinozaki A, Nagao T, Endo H, et al. Sebaceous Epithelial-Myoepithelial Carcinoma of the Salivary Gland: clinicopathologic and Immunohistochemical Analysis of 6 Cases of a New Histologic Variant. *Am J Surg Pathol* 2008; 32(6):913–923.
 22. Alòs L, Carrillo R, Ramos J, et al. High-grade carcinoma component in epithelial-myoepithelial carcinoma of salivary glands. Clinicopathological, immunohistochemical and flow-cytometric study of three cases. *Virchows Arch* 1999; 434(4):291–299.
 23. Fonseca I, Felix A, Soares J. Dedifferentiation in salivary gland carcinomas. *Am J Surg Pathol* 2000; 24(3):469–471.
 24. Daa T, Kashima K, Gamachi A, Nakayama I, et al. Epithelial-myoepithelial carcinoma harboring p53 mutation. *APMIS* 2001; 109(4):316–320.
 25. Kusafuka K, Takizawa Y, Ueno T et al. Dedifferentiated epithelial-myoepithelial carcinoma of the parotid gland: a rare case report of immunohistochemical analysis and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008 [Epub ahead of print]
 26. Daneshbod Y, Negahban S, Khademi B, et al. Epithelial myoepithelial carcinoma of the parotid gland with malignant ductal and myoepithelial components arising in a pleomorphic adenoma: a case report with cytologic, histologic and immunohistochemical correlation. *Acta Cytol* 2007; 51(5):807–813.
 27. Seifert G, Donath K. Hybrid tumours of salivary glands. Definition and classification of five rare cases. *Eur J Cancer Oral Oncol* 1996; 32B(4):251–259.
 28. Seifert G, Donath K. Multiple tumours of the salivary glands—terminology and nomenclature. *Eur J Cancer Oral Oncol* 1996; 32B(1):3–7.
 29. Grenko RT, Abendroth CS, Davis AT, et al. Hybrid tumors or salivary gland tumors sharing common differentiation pathways? Reexamining adenoid cystic carcinoma and epithelial-myoepithelial carcinomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86(2):188–195.
 30. Nagao T, Sugano I, Ishida Y, et al. Hybrid carcinomas of the salivary glands: report of nine cases with a clinicopathologic, immunohistochemical, and p53 gene alteration analysis. *Mod Pathol* 2002; 15(7):724–733.
 31. Chetty R, Medley P, Essa A. Hybrid carcinomas of salivary glands. *Arch Pathol Lab Med* 2000; 124(4):494–496.

Epithelial-Myoepithelial Carcinoma

1. Fonseca I, Soares J. Epithelial-myoepithelial carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:225–226.
2. Corridan M. Glycogen-rich clear-cell adenoma of the parotid gland. *J Pathol Bacteriol* 1956; 72:623–626.
3. Saksela E, Tarkkanen J, Wartiovaara J. Parotid clear cell adenoma of possible myoepithelial origin. *Cancer* 1972; 30(3):742–748.
4. Goldman RL, Klein HZ. Glycogen-rich adenoma of the parotid gland. An uncommon benign clear-cell tumor resembling certain clear-cell carcinomas of salivary origin. *Cancer* 1972; 30(3):749–754.
5. Batsakis JG. Clear cell tumors of salivary glands. *Ann Otol Rhinol Laryngol* 1980; 89(2 pt 1):196–197.
6. Mohamed AH, Cherrick HM. Glycogen-rich adenocarcinoma of minor salivary glands. A light and electron microscopy study. *Cancer* 1975; 36(3):1057–1066.
7. Chen KT. Clear cell carcinoma of the salivary gland. *Hum Pathol* 1983; 14(1):91–93.
8. Corio RL, Sciubba JJ, Brannon RB, et al. Epithelial-myoepithelial carcinoma of intercalated duct origin: a clinicopathologic and ultrastructural assessment of sixteen cases. *Oral Surg Oral Med Oral Pathol* 1982; 53(3):280–287.
9. Bauer WH, Fox RA. Adenomyoepithelioma (cylindroma) of palatal mucous glands. *Arch Pathol* 1945; 39:96–102.
10. Donath K, Seifert G, Schmitz R. [Diagnosis and ultrastructure of the tubular carcinoma of salivary gland ducts. Epithelial-myoepithelial carcinoma of the intercalated ducts] *Virchows Arch A Pathol Anat Histopathol* 1972; 356(1):16–31.
11. Luna MA, Ordonez NG, Mackay B, et al. Salivary epithelial-myoepithelial carcinomas of intercalated ducts: a clinical, electron microscopic, and immunocytochemical study. *Oral Surg Oral Med Oral Pathol* 1985; 59(5):482–490.
12. Cho KJA, El-Nagar AK, Ordonez NG, et al. Epithelial-myoepithelial carcinoma of salivary glands. A clinicopathologic, DNA flow cytometric, and immunohistochemical study of Ki-67 and HER-2/neu oncogene. *Am J Clin Pathol* 1995; 103(4):432–437.

32. Croitoru CM, Suarez PA, Luna MA. Hybrid carcinomas of salivary glands. Report of 4 cases and review of the literature. *Arch Pathol Lab Med* 1999; 123(8):698-702.
33. Di Palma S. Epithelial-myoepithelial carcinoma with co-existing multifocal intercalated duct hyperplasia of the parotid gland. *Histopathology* 1994; 25(5):494-496.
34. Chetty R. Intercalated duct hyperplasia: possible relationship to epithelial-myoepithelial carcinoma and hybrid tumours of salivary gland. *Histopathology* 2000; 37(3): 260-263.
35. el-Naggar AK, Lovell M, Ordonez NG, et al. Multiple unrelated translocations in a metastatic epimyoepithelial carcinoma of the parotid gland. *Cancer Genet Cytogenet* 1998; 100(2):155-158.
36. Mitelman F, Johansson B, Mertens F, eds. Mitelman database of chromosome aberrations in cancer (2003). Available at: <http://cgap.nci.nih.gov/Chromosomes/Mitelman>.
37. Martins C, Fonseca I, Roque L, et al. Malignant salivary gland neoplasms: a cytogenetic study of 19 cases. *Eur J Cancer B Oral Oncol* 1996; 32B(2):128-132.
38. Kleist B, Poetsch M, Breitsprecher C, et al. Epithelial-myoepithelial carcinoma of the parotid gland-evidence of contrasting DNA patterns in two different histological parts. *Virchows Arch* 2003; 442(6):585-590.
39. Hamper K, Brugmann M, Koppermann R, et al. Epithelial-myoepithelial duct carcinoma of salivary glands: a follow-up and cytophotometric study of 21 cases. *J Oral Pathol Med* 1989; 18(5):299-304.
10. Simpson RH, Sarsfield PT, Clarke T, et al. Clear cell carcinoma of minor salivary glands. *Histopathology* 1990; 17(5):433-438.
11. Milchgrub S, Gnepp DR, Vuitch F, et al. Hyalinizing clear cell carcinoma of salivary gland. *Am J Surg Pathol* 1994; 18(1): 74-82.
12. O'Regan E, Shandilya M, Gnepp DR, et al. Hyalinizing clear cell carcinoma of salivary gland: an aggressive variant. *Oral Oncol* 2004; 40(3):348-352.
13. Hayashi K, Ohtsuki Y, Sonobe H, et al. Glycogen-rich clear cell carcinoma arising from minor salivary glands of the uvula. A case report. *Acta Pathol Jpn* 1988; 38(9): 1227-1234.
14. Ogawa I, Nikai H, Takata T, et al. Clear cell tumors of minor salivary gland origin. An immunohistochemical and ultrastructural analysis. *Oral Surg Oral Med Oral Pathol* 1991; 72(2):200-207.
15. Shrestha P, Yang LT, Liu BL, et al. Clear cell carcinoma of salivary glands: immunohistochemical evaluation of clear tumor cells. *Anticancer Res* 1994; 14(3A):825-836.
16. Chao TK, Tsai CC, Yeh SY, et al. Hyalinizing clear cell carcinoma of the hard palate. *J Laryngol Otol* 2004; 118 (5):382-384.
17. Felix A, Rosa JC, Nunes JF, et al. Hyalinizing clear cell carcinoma of salivary glands: a study of extracellular matrix. *Oral Oncol* 2002; 38(4):364-368.
18. Batsakis JG, el-Naggar AK, Luna MA. Hyalinizing clear cell carcinoma of salivary origin. *Ann Otol Rhinol Laryngol* 1994; 103(9):746-748.
19. Grenevicki LF, Barker BF, Fiorella RM, et al. Clear cell carcinoma of the palate. *Int J Oral Maxillofac Surg* 2001; 30 (5):452-454.

Clear Cell Carcinoma, Not Otherwise Specified

1. Ellis GL. Clear cell carcinoma, not otherwise specified. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:227-228.
2. Ellis GL, Auclair PL. Clear cell carcinoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:379-389.
3. Ellis GL, Auclair PL. Clear cell adenocarcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:251-257.
4. Suzuki H, Yamauchi G, Hashimoto K. Clear cell carcinoma of the mandibular gingiva 'minor salivary gland': a case report with immunohistochemical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(3): e36-e40.
5. Rinaldo A, McLaren KM, Boccato P, et al. Hyalinizing clear cell carcinoma of the oral cavity and of the parotid gland. *ORL J Otorhinolaryngol Relat Spec* 1999; 61(1):48-51.
6. Wang B, Brandwein M, Gordon R, et al. Primary salivary clear cell tumors—a diagnostic approach: a clinicopathologic and immunohistochemical study of 20 patients with clear cell carcinoma, clear cell myoepithelial carcinoma, and epithelial-myoepithelial carcinoma. *Arch Pathol Lab Med* 2002; 126(6):676-685.
7. Berho M, Huvos AG. Central hyalinizing clear cell carcinoma of the mandible and the maxilla a clinicopathologic study of two cases with an analysis of the literature. *Hum Pathol* 1999; 30(1):101-105.
8. Negahban S, Daneshbod Y, Shishegar M. Clear cell carcinoma arising from pleomorphic adenoma of a minor salivary gland: report of a case with fine needle aspiration, histologic and immunohistochemical findings. *Acta Cytol* 2006; 50(6):687-690.
9. Uri AK, Wetmore RF, Iozzo RV. Glycogen-rich clear cell carcinoma in the tongue. A cytochemical and ultrastructural study. *Cancer* 1986; 57(9):1803-1809.

Basal Cell Adenocarcinoma

1. Batsakis JG, Luna MA. Basaloid salivary carcinoma. *Ann Otol Rhinol Laryngol* 1991; 100(9 pt1):785-787.
2. Simpson PR, Rutledge JC, Shaefer SD, et al. Congenital hybrid basal cell adenoma-adenoid cystic carcinoma of the salivary gland. *Pediatr Pathol* 1986; 6(2-3):199-208.
3. Ellis GL. Basal cell adenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:229-230.
4. Ellis GL, Wiscovitch JG. Basal cell adenocarcinomas of the major salivary glands. *Oral Surg Oral Med Oral Pathol* 1990; 69(4):461-469.
5. Fonseca I, Soares J. Basal cell adenocarcinoma of minor salivary and seromucous glands of the head and neck region. *Semin Diagn Pathol* 1996; 13(2):128-137.
6. Muller S, Barnes L. Basal cell adenocarcinoma of the salivary glands: report of seven cases and review of the literature. *Cancer* 1996; 78(12):2471-2477.
7. Nagao T, Sugano I, Ishida Y, et al. Basal cell adenocarcinoma of the salivary glands: comparison with basal cell adenoma through assessment of cell proliferation, apoptosis, and expression of p53 and bcl-2. *Cancer* 1998; 82(3): 439-447.
8. Quddus MR, Henley JD, Affify AM, et al. Basal cell adenocarcinoma of the salivary gland: an ultrastructural and immunohistochemical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 87(4):485-492.
9. Jayakrishnan A, Elmalah I, Hussain K, et al. Basal cell adenocarcinoma in minor salivary glands. *Histopathology* 2003; 42(6):610-614.
10. Parashar P, Baron E, Papadimitriou JC, et al. Basal cell adenocarcinoma of the oral minor salivary glands: review of the literature and presentation of two new cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(1): 77-84.

11. Farrell T, Chang YL. Basal cell adenocarcinoma of minor salivary glands. *Arch Pathol Lab Med* 2007; 131(10):1602–1604.
12. Klima M, Wolfe SK, Johnson PE. Basal cell tumors of the parotid gland. *Arch Otolaryngol* 1978; 104(2):111–116.
13. Chomette G, Auriol M, Vaillant JM, et al. Basaloid carcinoma of salivary glands, variety of undifferentiated adenocarcinoma: immunohistochemical study of intermediate filament proteins in 24 cases. *J Pathol* 1991; 163(1):39–45.
14. Luna MA, Batsakis JG, Tortoledo ME, et al. Carcinomas ex monomorphic adenoma of salivary glands. *J Laryngol Otol* 1989; 103(8):756–759.
15. Ellis GL, Auclair PL. Basal cell adenocarcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:257–267.
16. Hyman BA, Scheithauer BW, Weiland LH, et al. Membranous basal cell adenoma of the parotid gland: malignant transformation in a patient with multiple dermal cylindromas. *Arch Pathol Lab Med* 1988; 112(2):209–211.
17. Williams SB, Ellis GL, Auclair PL. Immunohistochemical analysis of basal cell adenocarcinoma. *Oral Surg Oral Med Oral Pathol* 1993; 75(1):64–69.
18. Seifert G. Classification and differential diagnosis of clear and basal cell tumors of the salivary glands. *Semin Diagn Pathol* 1996; 13(2):95–103.
19. Nagao T, Sugano I, Ishida Y, et al. Primary large-cell neuroendocrine carcinoma of the parotid gland: immunohistochemical and molecular analysis of two cases. *Mod Pathol* 2000; 13(5):554–562.
20. Banks ER, Frierson HF Jr., Mills SE, et al. Basaloid squamous cell carcinoma of the head and neck: a clinicopathologic and immunohistochemical study of 40 cases. *Am J Surg Pathol* 1992; 16(10):939–946.
10. Diedhiou A, Cazals-Hatem D, Rondini E, et al. Sebaceous carcinoma of the submandibular gland: a case report. *Ann Pathol* 2001; 21(4):348–351.
11. Handschel J, Herbst H, Brand B, et al. Intraoral sebaceous carcinoma. *Br J Oral Maxillofac Surg* 2003; 41(2):84–87.
12. Baiocco R, Palma O, Locatelli G. Squamous carcinoma of the epiglottis with sebaceous differentiation. Report of a case. *Pathologica* 1995; 87(5):531–533.
13. Esnal Leal F, Garcia GM, Perez R, et al. Sebaceous carcinoma of the salivary gland. Report of two cases of infrequent location. *An Otorrinolaringol Ibero Am* 1997; 24(4):401–413.
14. Martinez-Madrigal F, Casiraghi O, Khattech A, et al. Hypopharyngeal sebaceous carcinoma: a case report. *Hum Pathol* 1991; 22(9):929–931.
15. Granström G, Aldenborg F, Jeppsson PH. Sebaceous carcinoma of the parotid gland: report of a case and review of the literature. *J Oral Maxillofac Surg* 1987; 45(8):731–733.

Sebaceous Lymphadenocarcinoma

1. Gnepp DR. Sebaceous lymphadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:231.
2. Ahn SH, Park SY. Sebaceous lymphadenocarcinoma of parotid gland. *Eur Arch Otorhinolaryngol* 2006; 263(10):940–942.
3. Gnepp DR, Brannon R. Sebaceous neoplasms of salivary gland origin. Report of 21 cases. *Cancer* 1984; 53(10):2155–2170.
4. Linhartova A. Sebaceous glands in salivary gland tissue. *Arch Pathol* 1974; 98(5):320–324.
5. Croitoru CM, Mooney JE, Luna MA. Sebaceous lymphadenocarcinoma of salivary glands. *Ann Diagn Pathol* 2003; 7(4):236–239.

Sebaceous Carcinoma

1. Gnepp DR. Sebaceous carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:231.
2. Ellis GL, Auclair PL. Sebaceous adenocarcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:333–334.
3. Gnepp DR, Brannon R. Sebaceous neoplasms of salivary gland origin. Report of 21 cases. *Cancer* 1984; 53(10):2155–2170.
4. Gnepp DR. Sebaceous neoplasms of salivary gland origin: a review. *Pathol Annu* 1983; 18(pt 1):71–102.
5. Ellis GL, Auclair PL, Gnepp DR, et al. Other malignant epithelial neoplasms. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:471–476.
6. Mighell AJ, Stassen LF, Soames JV. Sebaceous carcinoma of the parotid gland. *Dentomaxillofac Radiol* 1996; 25(1):51–53.
7. Ohara N, Taguchi K, Yamamoto M, et al. Sebaceous carcinoma of the submandibular gland with high-grade malignancy: report of a case. *Pathol Int* 1998; 48(4):287–291.
8. Siriwardena BS, Tilakaratne WM, Rajapakshe RM. A case of sebaceous carcinoma of the parotid gland. *J Oral Pathol Med* 2003; 32(2):121–123.
9. Cohn ML, Callender DL, El-Naggar AK. Sebaceous carcinoma ex-pleomorphic adenoma: a rare phenotypic occurrence. *Ann Diagn Pathol* 2004; 8(4):224–226.

Cystadenocarcinoma

1. Seifert G, Sobin L. *World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours*. Berlin: Springer-Verlag, 1991.
2. Rawson AJ, Howard JM, Royster HP, et al. Tumors of the salivary glands; a clinicopathological study of 160 cases. *Cancer* 1950; 3(3):445–458.
3. Blanck C, Eneroth CM, Jakobsson PA. Mucus-producing adenopapillary (non-epidermoid) carcinoma of the parotid gland. *Cancer* 1971; 28(3):676–685.
4. Kardos TB, Ferguson JW, McMillan MD. Mucus-producing adenopapillary carcinoma of the oral cavity. *Int J Oral Maxillofac Surg* 1992; 21(3):160–162.
5. Allen MS Jr., Fitz-Hugh GS, March WL Jr. Low-grade papillary adenocarcinoma of the palate. *Cancer* 1974; 33(1):153–158.
6. Mills SE, Garland TA, Allen MS Jr. Low-grade papillary adenocarcinoma of palatal salivary gland origin. *Am J Surg Pathol* 1984; 8(5):367–374.
7. Spiro RH, Huvos AG, Strong EW. Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients. *Am J Surg* 1982; 144(4):423–431.
8. Auclair PL. Cystadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Head and Neck*. Lyon: IARC Press, 2005:232.
9. Brandwein-Gensler MS, Gnepp DR. Low-grade cribriform cystadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of*

- Tumours: Pathology and Genetics of Tumours of the Head and Neck. Lyon: IARC Press, 2005:233.
10. Foss R, Ellis G, Auclair P. Salivary gland cystadenocarcinomas: a clinicopathologic study of 57 cases. *Am J Surg Pathol* 1996; 20(12):1440-1447.
 11. Pollett A, Perez-Ordóñez B, Jordan RCK, et al. High-grade papillary cystadenocarcinoma of the tongue. *Histopathology* 1997; 31(2):185-188.
 12. Cavalcante RB, da Costa Miguel MC, Souza Carvalho AC, et al. Papillary cystadenocarcinoma: report of a case of high-grade histopathologic malignancy. *Auris Nasus Larynx* 2007; 34(2):259-262.
 13. Shrestha P, Namba M, Yang L, et al. Papillary cystadenocarcinoma of salivary glands: an immunohistochemical study. *Int J Oncol* 1994; 4:587-597.
 14. Kobayashi I, Kiyoshima T, Ozeki S, et al. Immunohistochemical and ultrastructural study of a papillary cystadenocarcinoma arising from the sublingual gland. *J Oral Pathol Med* 1999; 28(6):282-286.
 15. Delgado R, Klimstra D, Albores-Saavedra J. Low grade salivary duct carcinoma. A distinctive variant with low grade histology and a predominant intraductal growth pattern. *Cancer* 1996; 78(5):958-967.
 16. Brandwein-Gensler M, Hille J, Wang BY, et al. Low-Grade Salivary Duct Carcinoma. Description of 16 Cases. *Am J Surg Pathol* 2004; 28(4):1040-1044.
 17. Brandwein-Gensler MS, Skálová A, Nagao T. Salivary duct carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Head and Neck*. Lyon: IARC Press, 2005:236-237.
 18. Cheuk W, Miliauskas JR, Chan JK. Intraductal carcinoma of the oral cavity: a case report and a reappraisal of the concept of pure ductal carcinoma in situ in salivary duct carcinoma. *Am J Surg Pathol* 2004; 28(2):266-270.
 19. Weinreb I, Tabanda-Lichauco R, van der Kwast T, et al. Low-grade intraductal carcinoma of salivary gland: report of 3 cases with marked apocrine differentiation. *Am J Surg Pathol* 2006; 30(8):1014-1021.
 20. Tatemoto Y, Ohno A, Osaki T. Low malignant intraductal carcinoma on the hard palate: a variant of salivary duct carcinoma?. *Eur J Cancer B Oral Oncol* 1996; 32B(4):275-277.

Mucinous Adenocarcinoma

1. Sun KH, Goa Y, Li TJ. Mucinous adenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:234.
2. Gnepp D, Estalilla O, Henley J, et al. Primary colloid (mucinous) carcinoma of the salivary glands. *Oral Surg Oral Med Oral Pathol* 1997; 84(188) (abstr).
3. Gao Y, Di P, Peng X, et al. Mucinous adenocarcinoma of salivary glands. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2002; 37(5):356-358.
4. Krogdahl AS, Schou C. Mucinous adenocarcinoma of the sublingual gland. *J Oral Pathol Med* 1997; 26(4):198-200.
5. Tambouret RH, Yantiss RK, Kirby R, et al. Mucinous adenocarcinoma of the parotid gland. Report of a case with fine needle aspiration findings and histologic correlation. *Acta Cytol* 1999; 43(5):842-846.
6. Notani K, Iizuka T, Yamazaki Y, et al. Mucinous adenocarcinoma of probable minor salivary gland origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 94(6):738-740.
7. Hashitani S, Sakurai K, Noguchi K, et al. Mucinous adenocarcinoma with neuroendocrine differentiation of the mandibular ramus: report of a case. *J Oral Pathol Med* 2004; 33(1):59-63.

8. Osaki T, Hirota J, Ohno A, et al. Mucinous adenocarcinoma of the submandibular gland. *Cancer* 1990; 66(8):1796-1801.
9. Simpson RH, Prasad AR, Lewis JE, et al. Mucin-rich variant of salivary duct carcinoma: a clinicopathologic and immunohistochemical study of four cases. *Am J Surg Pathol* 2003; 27(8):1070-1079.

Oncocytic Carcinoma

1. Sciubba JJ, Shimono M. Oncocytic carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:235.
2. Auclair PL, Ellis GL, Gnepp DR, et al. Salivary gland neoplasms: general considerations. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:135-164.
3. Ellis GL, Auclair PL. Oncocytic carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:318-324.
4. Brandwein MS, Huvos AG. Oncocytic tumors of major salivary glands. A study of 68 cases with follow-up of 44 patients. *Am J Surg Pathol* 1991; 15(6):514-528.
5. Coli A, Bigotti G, Bartolazzi A. Malignant oncocytoma of the major salivary glands. Report of a post-radiation case. *J Exp Clin Cancer Res* 1998; 17(1):65-70.
6. Mahnke CG, Janig U, Werner JA. Metastasizing malignant oncocytoma of the submandibular gland. *J Laryngol Otol* 1998; 112(1):106-109.
7. Nakada M, Nishizaki K, Akagi H, et al. Oncocytic carcinoma of the submandibular gland: a case report and literature review. *J Oral Pathol Med* 1998; 27(5):225-228.
8. Gray SR, Cornog JL, Sei IS. Oncocytic neoplasms of salivary glands: a report of 15 cases including two malignant oncocytomas. *Cancer* 1976; 38(3):1306-1317.
9. Goode RK, Corio RL. Oncocytic adenocarcinoma of salivary glands. *Oral Surg Oral Med Oral Pathol* 1988; 65(1): 61-66.
10. Haberman RS, Rodger WA, Haberman PH. Malignant oncocytic adenocarcinoma of the parotid gland with metastasis to bone. *Surg Pathol* 1990; 3:221-226.
11. Sikorowa L. Oncocytoma malignum. *Nowotwory* 1957; 7:125-131.
12. Felix A, Fonseca I, Soares J. Oncocytic tumors of salivary gland type: a study with emphasis on nuclear DNA ploidy. *J Surg Oncol* 1993; 52(4):217-222.
13. Sugimoto T, Wakizono S, Uemura T, et al. Malignant oncocytoma of the parotid gland: a case report with an immunohistochemical and ultrastructural study. *J Laryngol Otol* 1993; 107(1):69-74.
14. Ardekian L, Manor R, Peled M, et al. Malignant oncocytoma of the parotid gland: case report and analysis of the literature. *J Oral Maxillofac Surg* 1999; 57(3):325-328.
15. Capone RB, Ha PK, Westra WH, et al. Oncocytic neoplasms of the parotid gland: a 16-year institutional review. *Otolaryngol Head Neck Surg* 2002; 126(6):657-662.
16. Cinar U, Vural C, Basak T, et al. Oncocytic carcinoma of the parotid gland: report of a new case. *Ear Nose Throat J* 2003; 82(9):699-701.
17. Muramatsu T, Hashimoto S, Lee MW, et al. Oncocytic carcinoma arising in submandibular gland with immunohistochemical observations and review of the literature. *Oral Oncol* 2003; 39(2):199-203.
18. Guclu E, Oghan F, Ozturk O, et al. A rare malignancy of the parotid gland: oncocytic carcinoma. *Eur Arch Otorhinolaryngol* 2005; 262(7):567-569.
19. Foschini MP, Malvi D, Betts CM. Oncocytic carcinoma arising in Warthin tumour. *Virchows Arch* 2005; 446(1):88-90.

20. Sugiyama T, Nakagawa T, Narita M, et al. Pedunculated oncocytic carcinoma in buccal mucosa: immunohistochemical and ultrastructural studies. *Oral Dis* 2006; 12(3): 324–328.
 21. Ito K, Tsukuda M, Kawabe R, et al. Benign and malignant oncocytoma of the salivary glands with an immunohistochemical evaluation of Ki-67. *ORL J Otorhinolaryngol Relat Spec* 2000; 62(6):338–341.
 22. Kimura M, Furuta T, Hashimoto S, et al. Oncocytic carcinoma of the parotid gland. A case report. *Acta Cytol* 2003; 47(6):1099–1102.
 23. Felix A, Fonseca I, Soares J. Oncocytic tumors of salivary gland type: a study with emphasis on nuclear DNA ploidy. *Surg Oncol* 1993; 52(4):217–222.
 24. Jahan-Parwar, Huberman RM, Donovan DT, et al. Oncocytic mucoepidermoid carcinoma of the salivary glands. *Am J Surg Pathol* 1999; 23(9):523–529.
 25. Brannon RB, Willard CC. Oncocytic mucoepidermoid carcinoma of parotid gland origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96(6):727–733.
 26. Kapadia SB, Barnes L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. *Mod Pathol* 1998; 11(11):1033–1038.
 27. Jensen ML. Multifocal adenomatous oncocytic hyperplasia in parotid glands with metastatic deposits or primary malignant transformation? *Pathol Res Pract* 1989; 185(4): 514–521.
 28. Johns ME, Regezi JA, Batsakis JG. Oncocytic neoplasms of salivary glands. An ultrastructural study. *Laryngoscope* 1977; 87(6):262–271.
- Salivary Duct Carcinoma*
1. Brandwein-Gensler MS, Skálová A, Nagao T. Salivary duct carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:236–237.
 2. Kleinsasser O, Klein HJ, Hübner G. Speicheldrüsencarcinome: ein den Milchgangcarcinomen der Brustdrüse analoge Gruppe von Speicheldrüsencarcinomen. *Arch Klin Exp Ohre Nasen Kehlkopfheilkd* 1968; 192(1):100–105.
 3. Seifert G, Sobin LH. *World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours*. 2nd ed. Berlin:Springer-Verlag, 1991.
 4. Brandwein MS, Jagirdar J, Patil J, et al. Salivary duct carcinoma (cribriform salivary carcinoma of excretory ducts): a clinicopathologic and immunohistochemical study of 12 cases. *Cancer* 1990; 65(10):2307–2314.
 5. Delgado R, Vuitch F, Albores-Saavedra J. Salivary duct carcinoma. *Cancer* 1993; 72(5):1503–1512.
 6. Barnes L, Rao U, Krause J, et al. Salivary duct carcinoma: Part I. A clinicopathologic evaluation and DNA image analysis of 13 cases with review of the literature. *Oral Surg Oral Med Oral Pathol* 1994; 78(1):64–73.
 7. Lewis JE, McKinney BC, Weiland LH, et al. Salivary duct carcinoma: clinicopathologic and immunohistochemical review of 26 cases. *Cancer* 1996; 77(2):223–230.
 8. Guzzo M, Di Palma S, Grandi C, et al. Salivary duct carcinoma: clinical characteristics and treatment strategies. *Head Neck* 1997; 19(2):126–133.
 9. Van Heerden WF, Raubenheimer EJ, Swart TJ, et al. Intraoral salivary duct carcinoma: a report of 5 cases. *J Oral Maxillofac Surg* 2003; 61(1):126–131.
 10. Jaehne M, Roeser K, Jaekel T, et al. Clinical and immunohistologic typing of salivary duct carcinoma: a report of 50 cases. *Cancer* 2005; 103(12):2526–2533.
 11. Ellis GL, Auclair PL. Salivary duct carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd Series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:324–333.
 12. Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: pathologic analysis of 77 cases. *Hum Pathol* 2001; 32(6):596–604.
 13. Nagao T, Sugano I, Ishida Y, et al. Hybrid carcinomas of the salivary glands: report of nine cases with a clinicopathologic, immunohistochemical, and p53 gene alteration analysis. *Mod Pathol* 2002; 15(7):724–733.
 14. Kapadia SB, Barnes L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. *Mod Pathol* 1998; 11(11):1033–1038.
 15. Wick MR, Ockner DM, Mills SE, et al. Homologous carcinomas of the breasts, skin, and salivary glands: a histologic and immunohistochemical comparison of ductal mammary carcinoma, ductal sweat gland carcinoma, and salivary duct carcinoma. *Am J Clin Pathol* 1998; 109(1):75–84.
 16. Fan CY, Wang J, Barnes EL. Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma: an immunohistochemical analysis of 13 cases and review of the literature. *Am J Surg Pathol* 2000; 24(4): 579–586.
 17. Skálová A, Stárek I, Vanecek T, et al. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. *Histopathology* 2003; 42(4):348–356.
 18. Glisson B, Colevas AD, Haddad R, et al. HER2 expression in salivary gland carcinoma: dependence on histological subtype. *Clin Cancer Res* 2004; 10(3):944–946.
 19. Cornolti G, Ungari M, Morassi ML, et al. Amplification and overexpression of HER2/neu gene and HER2/neu protein in salivary duct carcinoma of the parotid gland. *Arch Otolaryngol Head Neck Surg* 2007; 133(10):1031–1036.
 20. Johnson CJ, Barry MB, Vasef MA, et al. Her-2/neu expression in salivary duct carcinoma: an immunohistochemical and chromogenic in situ hybridization study. *Appl Immunohistochem Mol Morphol* 2008; 16(1):54–58.
 21. de Araújo VC, Kowalski LP, Soares F, et al. Salivary duct carcinoma: cytokeratin 14 as a marker of in-situ intraductal growth. *Histopathology* 2002; 41(3):244–249.
 22. Henley JD, Seo IS, Dayan D, et al. Sarcomatoid salivary duct carcinoma of the parotid gland. *Hum Pathol* 2000; 31(2):208–213.
 23. Ide F, Mishima K, Saito I. Sarcomatoid salivary duct carcinoma of the oral cavity. *Virchows Arch* 2003; 443(5):686–689.
 24. Nagao T, Gaffey TA, Serizawa H, et al. Sarcomatoid variant of salivary duct carcinoma: clinicopathologic and immunohistochemical study of eight cases with review of the literature. *Am J Clin Pathol* 2004; 122(2):222–231.
 25. Padberg BC, Sasse B, Huber A, et al. Sarcomatoid salivary duct carcinoma. *Ann Diagn Pathol* 2005; 9(2):86–92.
 26. Jeong HS, Son YI, Ko YH, et al. Sarcomatoid salivary duct carcinoma of the larynx. *J Laryngol Otol* 2006; 120(2):154–157.
 27. Simpson RHW, Prasad AR, Lewis JE, et al. Mucin-rich variant of salivary duct carcinoma: a clinicopathologic and immunohistochemical study of four cases. *Am J Surg Pathol* 2001; 27(8):1070–1079.
 28. Henley J, Summerlin DJ, Potter D, et al. Intraoral mucin-rich salivary duct carcinoma. *Histopathology* 2005; 47(4): 429–441.
 29. Nagao T, Gaffey TA, Visscher DW, et al. Invasive micro-papillary salivary duct carcinoma: a distinct histologic variant with biologic significance. *Am J Surg Pathol* 2004; 28(3):319–326.
 30. Delgado R, Klimstra D, Albores-Saavedra J. Low-grade salivary duct carcinoma: a distinctive variant with a low-grade

- histology and predominant intraductal growth pattern. *Cancer* 1996; 78(5):958–967.
31. Brandwein-Gensler M, Hille J, Wang BY, et al. Low-grade salivary duct carcinoma: description of 16 cases. *Am J Surg Pathol* 2004; 28(8):1040–1044.
 32. Brandwein-Gensler MS, Gnepp DR. Low-grade cribriform cystadenocarcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Head and Neck Tumours*. Lyon: IARC Press, 2005:233.
 33. Nassar H. Carcinomas with micropapillary morphology: clinical significance and current concepts. *Adv Anat Pathol* 2004; 11(6):297–303.
 34. Williams MD, Roberts D, Blumenschein GR Jr., et al. Differential expression of hormonal and growth factor receptors in salivary duct carcinomas: biologic significance and potential role in therapeutic stratification of patients. *Am J Surg Pathol* 2007; 31(11):1645–1652.
 35. Felix A, El-Naggar AK, Press MF, et al. Prognostic significance of biomarkers (c-erbB-2, p53, proliferating cell nuclear antigen, and DNA content) in salivary duct carcinoma. *Hum Pathol* 1996; 27(6):561–566.
 36. Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol* 2006; 24(17):2673–2678.
 37. Nabili V, Tan JW, Bhuta S, et al. Salivary duct carcinoma: a clinical and histologic review with implications for trastuzumab therapy. *Head Neck* 2007; 29(10):907–912.
 11. Spiro RH, Huvos AG, Strong EW. Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients. *Am J Surg* 1982; 144(4):423–431.
 12. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies on adenocarcinoma of the parotid gland. *Acta Pathol Jpn* 1986; 36(3):337–347.
 13. Matsuba HM, Mauney M, Simpson JR, et al. Adenocarcinomas of major and minor salivary gland origin: a histopathologic review of treatment failure patterns. *Laryngoscope* 1988; 98(7):784–788.
 14. Wahlberg P, Anderson H, Biörklund A, et al. Carcinoma of the parotid and submandibular glands—a study of survival in 2465 patients. *Oral Oncol* 2002; 38(7):706–713.

Myoepithelial Carcinoma

Adenocarcinoma, Not Otherwise Specified

1. Auclair P, van der Wal JE. Adenocarcinoma, not otherwise specified. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Head and Neck*. Lyon: IARC Press, 2005:238–239.
2. Thackray AC, Sobin LH. *World Health Organization International Histological Classification of Tumours: Histological Typing of Salivary Gland Tumours*. Berlin: Springer-Verlag, 1972.
3. Seifert G, Sobin LH. *World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours*. 2nd ed. Berlin: Springer-Verlag, 1991.
4. Batsakis JG, El Naggar AK, Luna MA. “Adenocarcinoma, not otherwise specified”: a diminishing group of salivary carcinomas. *Ann Otol Rhinol Laryngol* 1992; 101(1):102–104.
5. Van der Wal JE, Snow GB, van der Waal I. Histological reclassification of 101 intraoral salivary gland tumors (new WHO classification). *J Clin Pathol* 1992; 45(9):834–835.
6. Cesinaro AM, Crisculol M, Collina G, et al. Salivary gland tumors: revision of 391 cases according to the new WHO classification. *Pathologica* 1994; 86(6):602–605.
7. Van der Wal J, Leverstein H, Snow GB, et al. Parotid gland tumors: histologic reevaluation and reclassification of 478 cases. *Head Neck* 1998; 20(3):204–207.
8. Li J, Wang BY, Nelson M, et al. Salivary adenocarcinoma, not otherwise specified: a collection of orphans. *Arch Pathol Lab Med* 2004; 128(12):1385–1394.
9. Ellis GL, Auclair PL. Adenocarcinoma, not otherwise specified. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*, 3rd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:175–183.
10. Ghannoum JE, Freedman PD. Signet-ring cell (mucin-producing) adenocarcinoma of minor salivary glands. *Am J Surg Pathol* 2004; 28(1):89–93.
1. Stromeier FW, Haggitt RC, Nelson JF, et al. Myoepithelioma of minor salivary gland origin. Light and electron microscopical study. *Arch Pathol* 1975; 99(5):242–245.
2. Seifert G, Sobin L. *World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours* 2nd ed. Berlin: Springer-Verlag, 1991.
3. Skálová A, Jäkel KT. Myoepithelial carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:240–241.
4. Ellis GL, Auclair PL. Myoepithelial carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd Series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:337–343.
5. Saveria AT, Sloman A, Huvos A, et al. Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 25 cases. *Am J Surg Pathol* 2000; 24(6):761–774.
6. Crissman JD, Wirman JA, Harris A. Malignant myoepithelioma of the parotid gland. *Cancer* 1977; 40(6):3042–3049.
7. Di Palma S, Guzzo M. Malignant myoepithelioma of salivary glands: clinicopathological features of ten cases. *Virchows Arch A Pathol Anat Histopathol* 1993; 423(5):389–396.
8. El-Mofty SK, O’Leary TR, Swanson PE. Malignant myoepithelioma of salivary glands: clinicopathologic and immunophenotypic features. Review of literature and report of two cases. *Int J Surg Pathol* 1994; 2:133–140.
9. Alós L, Cardesa A, Bombi JA, et al. Myoepithelial tumors of salivary glands: a clinicopathologic, immunohistochemical, ultrastructural, and flow-cytometric study. *Semin Diagn Pathol* 1996; 13(2):138–147.
10. Michal M, Skálová A, Simpson RHW, et al. Clear cell malignant myoepithelioma of the salivary glands. *Histopathology* 1996; 28(4):309–315.
11. Nagao T, Sugano I, Ishida Y, et al. Salivary gland malignant myoepithelioma: a clinicopathologic and immunohistochemical study of 10 cases. *Cancer* 1998; 83(7):1292–1299.
12. Chhieng DC, Paulino AF. Cytology of myoepithelial carcinoma of the salivary gland. *Cancer* 2002; 96(1):32–36.
13. Hungermann D, Roeser K, Buerger H, et al. Relative paucity of gross genetic alterations in myoepitheliomas and myoepithelial carcinomas of salivary glands. *J Pathol* 2002; 198(4):487–494.
14. Losito NS, Botti G, Ionna F, et al. Clear-cell myoepithelial carcinoma of the salivary glands: a clinicopathologic, immunohistochemical, and ultrastructural study of two cases involving the submandibular gland with review of the literature. *Pathol Res Pract* 2008; 204(5):335–344.

15. Graadt van Roggen JF, Baatenberg-de Jong RJ, Verschuur HP, et al. Myoepithelial carcinoma (malignant myoepithelioma): first report of an occurrence in the maxillary sinus. *Histopathology* 1998; 32(3):239–241.
16. Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. *Am J Surg Pathol* 2007; 31(1):44–57.
17. Ogawa I, Nishida T, Miyauchi M, et al. Dedifferentiated malignant myoepithelioma of the parotid gland. *Pathol Int* 2003; 53(10):704–709.
18. Seifert G. Classification and differential diagnosis of clear and basal cell tumors of the salivary glands. *Semin Diagn Pathol* 1996; 13(2):95–103.
19. Wang B, Brandwein M, Gordon R, et al. Primary salivary gland clear cell tumors—a diagnostic approach: a clinicopathologic and immunohistochemical study of 20 patients with clear cell carcinoma, clear cell myoepithelial carcinoma, and epithelial-myoepithelial carcinoma. *Arch Pathol Lab Med* 2002; 126(6):676–685.
20. El-Naggar A, Batsakis JG, Luna MA, et al. DNA content and proliferative activity of myoepitheliomas. *J Laryngol Otol* 1989; 103(12):1192–1197.
21. Carrillo R, El-Naggar AK, Luna MA, et al. Nucleolar organizer regions (NORs) and myoepitheliomas: a comparison with DNA content and clinical course. *J Laryngol Otol* 1992; 106(7):616–620.
12. Klijanienko J, El-Naggar AK, Servois V, et al. Mucoepidermoid carcinoma ex pleomorphic adenoma: nonspecific preoperative cytologic findings in six cases. *Cancer* 1998; 84(4):231–234.
13. Ihrler S, Weiler C, Hirschmann A, et al. Intraductal carcinoma is the precursor of carcinoma ex pleomorphic adenoma and is often associated with dysfunctional p53. *Histopathology* 2007; 51(3):362–371.
14. Altmani A, Martins MT, Freitas L, et al. Carcinoma ex pleomorphic adenoma (CXPA): immunoprofile of the cells involved in carcinomatous progression. *Histopathology* 2005; 46(6):635–641.
15. Luna MA, Batsakis JG, Tortoledo ME, et al. Carcinomas ex monomorphic adenoma of salivary glands. *J Laryngol Otol* 1989; 103(8):756–759.
16. Di Palma S, Skalova A, Vanieek T. Non-invasive (intra-capsular) carcinoma ex pleomorphic adenoma: recognition of focal carcinoma by HER-2/neu and MIB1 immunohistochemistry. *Histopathology* 2005; 46(2):144–152.
17. Rao PH, Murty VV, Louie DC, et al. Nonsyntenic amplification of MYC with CDK4 and MDM2 in a malignant mixed tumor of salivary gland. *Cancer Genet Cytogenet* 1998; 105(2):160–163.
18. Roijer E, Nordkvist A, Strom AK, et al. Translocation, deletion/amplification, and expression of HMGIC and MDM2 in a carcinoma ex pleomorphic adenoma. *Am J Pathol* 2002; 160(2):433–440.
19. El-Naggar AK, Callender D, Coombes MM. Molecular genetic alterations in carcinoma ex-pleomorphic adenoma: a putative progression model? *Genes Chromosomes Cancer* 2000; 27(2):162–168.
20. Gillenwater A, Hurr K, Wolf P, et al. Microsatellite alterations at chromosome 8q loci in pleomorphic adenoma. *Otolaryngol Head Neck Surg* 1997; 117(5):448–452.
21. Ohtake S, Cheng J, Ida H, et al. Precancerous foci in pleomorphic adenoma of the salivary gland: recognition of focal carcinoma and atypical tumor cells by P53 immunohistochemistry. *J Oral Pathol Med* 2002; 31(10): 590–597.
22. Freitas LL, Arajo VC, Martins MT, et al. Biomarker analysis in carcinoma ex pleomorphic adenoma at an early phase of carcinomatous transformation. *Int J Surg Pathol* 2005; 13(4):337–342.
23. Suzuki H, Fujioka Y. Deletion of the p16 gene and microsatellite instability in carcinoma arising in pleomorphic adenoma of the parotid gland. *Diagn Mol Pathol* 1998; 7(4):224–231.
24. Felix A, Rosa-Santos J, Mendonca ME. Intracapsular carcinoma ex pleomorphic adenoma. Report of a case with unusual metastatic behaviour. *Oral Oncol* 2002; 38(1): 107–110.
25. Thomas WH, Coppola ED. Distant metastases from mixed tumors of the salivary glands. *Am J Surg* 1965; 109:724–730.

Carcinoma Ex Pleomorphic Adenoma

1. Gnepp DR, Brandwein-Gensler M, El-Naggar AK, et al. Carcinoma ex pleomorphic adenoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:242–243.
2. Gnepp DR. Malignant mixed tumors of the salivary glands: a review. *Pathol Annu* 1993; 28(pt 1):279–328.
3. Spiro RH, Huvo AG, Strong EW. Malignant mixed tumor of salivary origin: a clinicopathologic study of 146 cases. *Cancer* 1977; 39(2):388–396.
4. Foote FW Jr., Frazell EL. Tumors of the major salivary glands. *Cancer* 1953; 6(6):1065–1133.
5. Auclair PA, Ellis GL, Gnepp DR, et al. Salivary gland neoplasms: general considerations. In: Ellis GL, Auclair PA, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:144–145.
6. Gerughty RM, Scofield HH, Brown FM, et al. Malignant mixed tumors of salivary gland origin. *Cancer* 1969; 24(3): 471–486.
7. Eneroth CM, Zetterberg A. Malignancy in pleomorphic adenoma. A clinical and microspectrophotometric study. *Acta Otolaryngol* 1974; 77(6):426–432.
8. LiVolsi VA, Perzin KH. Malignant mixed tumors arising in salivary glands I. Carcinomas arising in benign mixed tumors: a clinicopathologic study. *Cancer* 1977; 39(5): 2209–2230.
9. Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: pathologic analysis of 73 cases. *Hum Pathol* 2001; 32(6):596–604.
10. Tortoledo ME, Luna MA, Batsakis JG. Carcinomas ex pleomorphic adenoma and malignant mixed tumors. *Arch Otolaryngol* 1984; 110(3):172–176.
11. Brandwein M, Huvo AG, Dardick I, et al. Noninvasive and minimally invasive carcinoma ex mixed tumor. A clinicopathologic and ploidy study of 12 patients with major salivary tumors of low (or no?) malignant potential. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 81(6):655–664.

Carcinosarcoma

1. Gnepp DR. Carcinosarcoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:244.
2. Gnepp DR. Malignant mixed tumors of the salivary glands: a review. *Pathol Annu* 1993; 28(pt 1):279–328.
3. Bleiweiss IJ, Huvo AG, Lara J, et al. Carcinosarcoma of the submandibular salivary gland. Immunohistochemical findings. *Cancer* 1992; 69(8):2031–2035.
4. Bocklage T, Feddersen R. Unusual mesenchymal and mixed tumors of the salivary gland. An immunohistochemical and flow cytometric analysis of three cases. *Arch Pathol Lab Med* 1995; 119(1):69–74.
5. Takata T, Nikai H, Ogawa I, et al. Ultrastructural and immunohistochemical observations of a true malignant

- mixed tumor (carcinosarcoma) of the tongue. *J Oral Pathol Med* 1990; 19(6):261–265.
6. Stephen J, Batsakis JG, Luna MA, et al. True malignant mixed tumors (carcinosarcoma) of salivary glands. *Oral Surg Oral Med Oral Pathol* 1986; 61(6):597–602.
 7. Garner SL, Robinson RA, Maves MD, et al. Salivary gland carcinosarcoma: true malignant mixed tumor. *Ann Otol Rhinol Laryngol* 1989; 98(8):611–614.
 8. Alvarez-Canas C, Rodilla IG. True malignant mixed tumor (carcinosarcoma) of the parotid gland. Report of a case with immunohistochemical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 81(4):454–458.
 9. Julie C, Aidan D, Arkwright S, et al. Carcinosarcoma of the submaxillary gland. *Ann Pathol* 1997; 17(1):35–37.
 10. Ueo T, Kaku N, Kashima K, et al. Carcinosarcoma of the parotid gland: an unusual case with large-cell neuroendocrine carcinoma and rhabdomyosarcoma. *APMIS* 2005; 113(6):456–464.
 11. Gotte K, Riedel F, Coy JF, et al. Salivary gland carcinosarcoma: immunohistochemical, molecular genetic and electron microscope findings. *Oral Oncol* 2000; 36(4):360–364.
 12. Kim T, Yoon GS, Kim O, et al. Fine needle aspiration diagnosis of malignant mixed tumor (carcinosarcoma) arising in pleomorphic adenoma of the salivary gland. A case report. *Acta Cytol* 1998; 42(4):1027–1031.
 13. Gogas J, Markopoulos C, Karydakis V, et al. Carcinosarcoma of the submandibular salivary gland. *Eur J Surg Oncol* 1999; 25(3):333–335.
 14. King AD, Ahuja AT, To EW. Carcinosarcoma of the parotid gland: ultrasound and computed tomography findings. *Australas Radiol* 1999; 43(4):520–522.
 15. Kwon MY, Gu M. True malignant mixed tumor (carcinosarcoma) of parotid gland with unusual mesenchymal component: a case report and review of the literature. *Arch Pathol Lab Med* 2001; 125(6):812–815.
 16. Sironi M, Isimbaldi G, Claren R. Carcinosarcoma of the parotid gland: cytological, clinicopathological and immunohistochemical study of a case. *Pathol Res Pract* 2000; 196(7):511–517.
 17. Thome Capuano AC, Dos Santos Pinto Junior D, Carvalho AA, et al. Immunoprofile of a carcinosarcoma of the submandibular gland. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(3):398–402.
 18. Fowler MH, Fowler J, Ducatman B, et al. Malignant mixed tumors of the salivary gland: a study of loss of heterozygosity in tumor suppressor genes. *Mod Pathol* 2006; 19(3):350–355.
 19. Morey-Mas M, Caubet-Biayna J, Gomez-Bellvert C, et al. Carcinosarcoma of the submandibular and sublingual salivary glands. A case report and review of the literature. *Acta Stomatol Belg* 1997; 94(2):69–73.
 20. Galli J, Parrilla C, Corina L et al. Carcinosarcoma of the submandibular salivary gland: clinical case and review of the literature. *J Otolaryngol* 2005; 34(1):66–69.
 21. Tanahashi J, Daa T, Kashima K, et al. Carcinosarcoma ex recurrent pleomorphic adenoma of the submandibular gland. *APMIS* 2007; 115(6):789–794.
 22. Staffieri C, Marioni G, Ferraro SM, et al. Carcinosarcoma de novo of the parotid gland. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(2):e35–e40.
 2. Nouraei SA, Ferguson MS, Clarke PM, et al. Metastasizing pleomorphic salivary adenoma. *Arch Otolaryngol Head Neck Surg* 2006; 132(7):788–793.
 3. Steele NP, Wenig BM, Sessions RB. A case of pleomorphic adenoma of the parotid gland metastasizing to a mediastinal lymph node. *Am J Otolaryngol* 2007; 28(2):130–133.
 4. Van der Schroeff MP, de Ru JA, Slootweg PJ. Case-report: metastasizing pleomorphic adenoma of the parotid gland. *B-ENT* 2007; 3(1):21–25.
 5. Bradley PJ. 'Metastasizing pleomorphic salivary adenoma' should now be considered a low-grade malignancy with a lethal potential. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13(2):123–126.
 6. Spiro RH, Huvos AG, Strong EW. Malignant mixed tumor of salivary origin: a clinicopathologic study of 146 cases. *Cancer* 1977; 39(2):388–396.
 7. Gnepp DR. Malignant mixed tumors of the salivary glands: a review. *Pathol Annu* 1993; 28(pt 1):279–328.
 8. Gnepp DR, Wenig BM. Malignant mixed tumors. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:350–368.
 9. Wenig BM, Hitchcock CL, Ellis GL, et al. Metastasizing mixed tumor of salivary glands. A clinicopathologic and flow cytometric analysis. *Am J Surg Pathol* 1992; 16(9):845–858.
 10. Hoorweg JJ, Hilgers FJM, Keus RB, et al. Metastasizing pleomorphic adenoma: a report of three cases. *Eur J Surg Oncol* 1998; 24(5):452–455.
 11. Goodisson DW, Buff RGM, Creedon AJ, et al. A case of metastasizing pleomorphic adenoma. *Oral Med Oral Surg Oral Pathol Oral Radiol Endod* 1999; 87(3):341–345.
 12. el-Naggar A, Batsakis JG, Kessler S. Benign metastatic mixed tumours or unrecognised salivary carcinomas. *J Laryngol Otol* 1988; 102(9):810–812.
 13. Jin Y, Jin C, Arheden K, et al. Unbalanced chromosomal rearrangements in a metastasizing salivary gland tumor with benign histology. *Cancer Genet Cytogenet* 1998; 102(1):59–64.

Squamous Cell Carcinoma

1. Lewis JE, Olsen KD. Squamous Cell Carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:245–246.
2. Sakurai K, Urade M, Kishimoto H, et al. Primary squamous cell carcinoma of the accessory parotid duct epithelium. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85(4):447–451.
3. Batsakis JG, McClatchey KD, Johns M, et al. Primary squamous cell carcinoma of the parotid gland. *Arch Otolaryngol* 1976; 102(6):55–57.
4. Batsakis JG. Primary squamous cell carcinoma of the major salivary glands. *Ann Otol Rhinol Laryngol* 1983; 92(1):97–98.
5. Gaughan RK, Olsen KD, Lewis JE. Primary squamous cell carcinoma of the parotid gland. *Arch Otolaryngol Head Neck Surg* 1992; 118(8):798–801.
6. Serman BM, Kraus DH, Sebek BA, et al. Primary squamous cell carcinoma of the parotid gland. *Laryngoscope* 1990; 100(2 pt 1):146–148.
7. Shemen LJ, Huvos AG, Spiro RH. Squamous cell carcinoma of salivary gland origin. *Head Neck Surg* 1987; 9(4):235–240.
8. Ying YL, Johnson JT, Myers EN. Squamous cell carcinoma of the parotid gland. *Head Neck* 2006; 28(7):626–632.
9. Hong TS, Kriesel KJ, Hartig GK, et al. Parotid area lymph node metastases from cutaneous squamous cell carcinoma: implications for diagnosis, treatment, and prognosis. *Head Neck* 2005; 27(10):851–856.

Metastasizing Pleomorphic Adenoma

1. Gnepp DR. Metastasizing pleomorphic adenoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:245.

10. Lee S-W, Kim GE, Park CS, et al. Primary squamous cell carcinoma of the parotid gland. *Am J Otolaryngol* 2001; 22(6):400–406.
11. Steiner M, Gould AR, Miller RL, et al. Malignant tumors of Stensen's duct. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 87(1):73–77.
12. Auclair PL, Ellis GL. Primary squamous cell carcinoma. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:369–378.
13. Cartei G, Zorat P, Cartei F, et al. Poorly differentiated squamous cell carcinoma of the parotid gland in a 13-year-old girl [letter]. *Med Pediatr Oncol* 1998; 30(6):374–375.
14. Ellis GL, Auclair PL. Primary squamous cell carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:251–257.
15. Sandros J, Mark J, Happonen RP, et al. Specificity of 6q-markers and other recurrent deviations in human malignant salivary gland tumors. *Anticancer Res* 1988; 8(4):637–643.
16. Mark J, Nordkvist A, Dahlenfors R, et al. Complex chromosomal changes in a primary squamous carcinoma of the parotid gland. *Anticancer Res* 1993; 13(4):897–899.
17. Jin Y, Mertens F, Mandahl N, et al. Tetraploidization and progressive loss of 6q in a squamous cell carcinoma of the parotid gland. *Cancer Genet Cytogenet* 1995; 79(2):157–159.
18. Nagao T, Serizawa H, Iwaya K, et al. Keratocystoma of the parotid gland: a report of two cases of an unusual pathologic entity. *Mod Pathol* 2002; 15(9):1005–1010.
19. Flynn MB, Maguire S, Martinez S, et al. Primary squamous cell carcinoma of the parotid gland: the importance of correct histological diagnosis. *Ann Surg Oncol* 1999; 6(8):768–770.
- neuroendocrine) carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites. *Am J Surg Pathol* 1997; 21(2):226–234.
10. Koss LG, Spiro RH, Hajdu S. Small cell (oat cell) carcinoma of minor salivary gland origin. *Cancer* 1972; 30(3):737–741.
11. Wirman JA, Battifora HA. Small cell undifferentiated carcinoma of salivary gland origin: an ultrastructural study. *Cancer* 1976; 37(4):1840–1848.
12. Kraemer BB, Mackay B, Batsakis JG. Small cell carcinomas of the parotid gland: a clinicopathologic study of three cases. *Cancer* 1983; 52(11):2115–2121.
13. Gnepp DR, Corio RL, Brannon RB. Small cell carcinoma of the major salivary glands. *Cancer* 1986; 58(3):705–714.
14. Huntrakoon M. Neuroendocrine carcinoma of the parotid gland: a report of two cases with ultrastructural and immunohistochemical studies. *Hum Pathol* 1987; 18(12):1212–1217.
15. Hayashi Y, Nagamine S, Yanagawa T, et al. Small cell undifferentiated carcinoma of the minor salivary gland containing exocrine, neuroendocrine, and squamous cells. *Cancer* 1987; 60(7):1583–1588.
16. Mair S, Phillips JI, Cohen R. Small cell undifferentiated carcinoma of the parotid gland: cytologic, histologic, immunohistochemical and ultrastructural features of a neuroendocrine variant. *Acta Cytol* 1989; 33(2):164–168.
17. Hui KK, Luna MA, Batsakis JG, et al. Undifferentiated carcinoma of the major salivary glands. *Oral Surg Oral Med Oral Pathol* 1990; 69(1):76–83.
18. Pierce ST, Cibull ML, Metcalfe MS, et al. Bone marrow metastases from small cell cancer of the head and neck. *Head Neck* 1994; 16(3):266–271.
19. Toyosawa S, Ohnishi A, Ito R, et al. Small cell undifferentiated carcinoma of the submandibular gland: immunohistochemical evidence of myoepithelial, basal and luminal cell features. *Pathol Int* 1999; 49(10):887–892.
20. Vural C, Dogan O, Yavuz E, et al. Small cell neuroendocrine tumor of the parotid gland. *Otolaryngol Head Neck Surg* 2000; 122(1):151–152.
21. Siciliano S, Crevecoeur H, Weynand B, et al. Primary neuroendocrine carcinoma of the parotid gland: a case report. *J Oral Maxillofac Surg* 2001; 59(11):1359–1362.
22. Mineta H, Miura K, Takebayashi S, et al. Immunohistochemical analysis of small cell carcinoma of the head and neck: a report of four patients and a review of sixteen patients in the literature with ectopic hormone production. *Ann Otol Rhinol Laryngol* 2001; 110(1):76–82.
23. de Vicente Rodríguez JC, Fresno Forcelledo MF, Junquera Gutiérrez LM, et al. Small cell undifferentiated carcinoma of the submandibular gland with neuroendocrine features. *Ann Otol Rhinol Laryngol* 2004; 113(1):55–59.
24. Cheuk W, Kwan MY, Suster S, et al. Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. *Arch Pathol Lab Med* 2001; 125(2):228–231.
25. Gnepp DR. Small cell neuroendocrine carcinoma of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec* 1991; 53(4):210–219.

Small Cell Carcinoma

1. Seifert G, Sobin L. *World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours*. 2nd ed. Berlin: Springer-Verlag, 1991.
2. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies of undifferentiated carcinoma of the parotid gland. *Cancer* 1982; 50(8):1572–1579.
3. Ellis GL, Auclair PL. Undifferentiated carcinomas. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:296–311.
4. Nagao T. Small cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:247–248.
5. Nagao T. Large cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:249–250.
6. Tsang WYW, Kuo TT, Chan JKC. Lymphoepithelial carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:251–252.
7. Gnepp DR, Wick MR. Small cell carcinoma of the major salivary glands: an immunohistochemical study. *Cancer* 1990; 66(1):185–192.
8. Nagao T, Gaffey TA, Olsen KD, et al. Small cell carcinoma of the major salivary gland: clinicopathologic study with emphasis on cytokeratin 20 immunoreactivity and clinical outcome. *Am J Surg Pathol* 2004; 28(6):762–770.
9. Chan JK, Suster S, Wenig BM, et al. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous

Large Cell Carcinoma

1. Nagao T. Large cell carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:249–250.
2. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies of undifferentiated carcinoma of the parotid gland. *Cancer* 1982; 50(8):1572–1579.

3. Hui KK, Luna MA, Batsakis JG, et al. Undifferentiated carcinomas of the major salivary glands. *Oral Surg Oral Med Oral Pathol* 1990; 69(1):76-83.
4. Batsakis JG, Luna MA. Undifferentiated carcinomas of salivary glands. *Ann Otol Rhinol Laryngol* 1991; 100(1): 82-84.
5. Moore JG, Bocklage T. Fine-needle aspiration biopsy of large-cell undifferentiated carcinoma of the salivary glands: presentation of two cases, literature review, and differential cytodiagnosis of high-grade salivary gland malignancies. *Diagn Cytopathol* 1998; 19(1):44-50.
6. Uemaetomari I, Ito Z. Large-cell undifferentiated carcinoma of the submandibular gland. *Auris Nasus Larynx* 2005; 32(4):431-434.
7. Seifert G, Sobin L. World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours. 2nd ed. Berlin: Springer-Verlag, 1991.
8. Larsson LG, Donner LR. Large cell neuroendocrine carcinoma of the parotid gland: fine needle aspiration, and light microscopic and ultrastructural study. *Acta Cytol* 1999; 43(3):534-536.
9. Nagao T, Sugano I, Ishida Y, et al. Primary large-cell neuroendocrine carcinoma of the parotid gland: immunohistochemical and molecular analysis of two cases. *Mod Pathol* 2000; 13(5):554-561.
10. Casas P, Bernáldez R, Patrón M, et al. Large cell neuroendocrine carcinoma of the parotid gland: case report and literature review. *Auris Nasus Larynx* 2005; 32(1):89-93.
11. Hayashi Y, Aoki N. Undifferentiated carcinoma of the parotid gland with bizarre giant cells: clinicopathologic report with ultrastructural study. *Acta Pathol Jpn* 1983; 33(1):169-176.
12. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies on carcinoma in pleomorphic adenoma of the parotid gland. *Cancer* 1981; 48(1):113-121.
13. Stanley RJ, Weiland LH, Olsen KD, et al. Dedifferentiated acinic cell (acinous) carcinoma of the parotid gland. *Otolaryngol Head Neck Surg* 1988; 98(2):155-161.
14. Nagao T, Gaffey TA, Kay PA, et al. Dedifferentiation in low-grade mucoepidermoid carcinoma of the parotid gland. *Hum Pathol* 2003; 34(10):1068-1072.
15. Nagao T, Gaffey TA, Serizawa H, et al. Dedifferentiated adenoid cystic carcinoma: a clinicopathologic study of 6 cases. *Mod Pathol* 2003; 16(12):1265-1272.
16. Alos L, Carrillo R, Ramos J, et al. High-grade carcinoma component in epithelial-myoepithelial carcinoma of salivary glands clinicopathological, immunohistochemical and flow-cytometric study of three cases. *Virchows Arch* 1999; 434(4):291-299.
17. Lloreta J, Serrano S, Corominas JM, et al. Polymorphous low-grade adenocarcinoma arising in the nasal cavities with an associated undifferentiated carcinoma. *Ultrastruct Pathol* 1995; 19(5):365-370.
18. Soini Y, Kamel D, Nuorva K, et al. Low p53 protein expression in salivary gland tumours compared with lung carcinomas. *Virchows Arch A Pathol Anat Histopathol* 1992; 421(3):415-420.
19. Mutoh H, Nagata H, Ohno K, et al. Analysis of the p53 gene in parotid gland cancers: a relatively high frequency of mutations in low-grade mucoepidermoid carcinomas. *Int J Oncol* 2001; 18(4):781-786.
20. Yaku Y, Kanda T, Yoshihara T, et al. Undifferentiated carcinoma of the parotid gland: case report with electron microscopic findings. *Virchows Arch A Pathol Anat Histopathol* 1983; 401(1):89-97.
21. Takata T, Caselitz J, Seifert G. Undifferentiated tumors of salivary glands: immunocytochemical investigations and differential diagnosis of 22 cases. *Pathol Res Pract* 1987; 182(2):161-168.
22. Wang CP, Chang YL, Ko JK, et al. Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands. *Cancer* 2004; 101(9):2020-2027.

Lymphoepithelial Carcinoma

1. Chan JKC, Yip TT, Tsang WY, et al. Specific association of Epstein-Barr virus with lymphoepithelial carcinoma among tumors and tumorlike lesions of the salivary gland. *Arch Pathol Lab Med* 1994; 118(10):994-997.
2. Leung SY, Chung LP, Yuen ST, et al. Lymphoepithelial carcinoma of the salivary gland: *in situ* detection of Epstein-Barr virus. *J Clin Pathol* 1995; 48(11):1022-1027.
3. Kountakis SE, SooHoo W, Maillard A. Lymphoepithelial carcinoma of the parotid gland. *Head Neck* 1995; 17(5):445-450.
4. Abdulla AK, Mian MY. Lymphoepithelial carcinoma of salivary glands. *Head Neck* 1996; 18(6):577-581.
5. Worley NK, Daroca PJ Jr. Lymphoepithelial carcinoma of the minor salivary gland. *Arch Otolaryngol Head Neck Surg* 1997; 123(6):638-640.
6. Wang CP, Chang YL, Ko JY, et al. Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands. *Cancer* 2004; 101(9):2020-2027.
7. Tsang WYW, Kuo TT, Chan JKC. Lymphoepithelial carcinoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumors*. Lyon: IARC Press, 2005:251-252.
8. Seifert G, Sobin LH. World Health Organization International Histologic Classification of Tumours: Histologic Typing of Salivary Gland Tumours. 2nd ed. Berlin: Springer-Verlag, 1991:30-31.
9. Cleary KR, Batsakis JG. Undifferentiated carcinoma with lymphoid stroma of the major salivary glands. *Ann Otol Rhinol Laryngol* 1990; 99(3 pt 1):236-238.
10. Nagao T, Ishida Y, Sugano I, et al. Epstein-Barr virus-associated undifferentiated carcinoma with lymphoid stroma of the salivary gland in Japanese patients: comparison with benign lymphoepithelial lesion. *Cancer* 1996; 78(4): 695-703.
11. Evans AT, Guthrie W. Lymphoepithelioma-like carcinoma of the uvula and palate: a rare lesion in an unusual site. *Histopathology* 1991; 19(2):184-186.
12. Kuo T, Hsueh C. Lymphoepithelioma-like salivary gland carcinoma in Taiwan: a clinicopathological study of nine cases demonstrating a strong association with Epstein-Barr virus. *Histopathology* 1997; 31(1):75-82.
13. Ferlito A, Donati LF. Malignant lymphoepithelial lesions (undifferentiated ductal carcinomas of the parotid gland). *J Laryngol Otol* 1977; 91(10):869-885.
14. Nagao K, Matsuzaki O, Saiga H, et al. A histopathologic study of benign and malignant lymphoepithelial lesions of the parotid gland. *Cancer* 1983; 52(6):1044-1052.
15. Yazdi HM, Hogg GR. Malignant lymphoepithelial lesion of the submandibular gland. *Am J Clin Pathol* 1984; 82(3): 344-348.
16. Saw D, Lau WH, Ho JH, et al. Malignant lymphoepithelial lesion of the salivary gland. *Hum Pathol* 1986; 17(9):914-923.
17. Bosch JD, Kudryk WH, Johnson GH. The malignant lymphoepithelial lesion of the salivary glands. *J Otolaryngol* 1988; 17(4):187-190.
18. Christiansen MS, Mourad WA, Hales ML, et al. Spindle cell malignant lymphoepithelial lesion of the parotid gland: clinical, light microscopic, ultrastructural, and *in situ* hybridization findings in one case. *Mod Pathol* 1995; 8(7):711-715.
19. Wu DLL, Shemen L, Brady T, et al. Malignant lymphoepithelial lesion of the parotid gland: a case report and review of the literature. *Ear Nose Throat J* 2001; 80(11):803-806.

20. Chen KTK. Carcinoma arising in a benign lymphoepithelial lesion. *Arch Otolaryngol* 1983; 109(9):619–621.
21. Wallace AG, McDougall JT, Hildes JA, et al. Salivary gland tumors in Canadian Eskimos. *Cancer* 1963; 16: 1338–1353.
22. Nielsen NH, Mikkelsen F, Hansen JP. Incidence of salivary gland neoplasms in Greenland with special reference to an anaplastic carcinoma. *Acta Path Microbiol Scand [A]* 1978; 86(2):185–193.
23. Saemundsen AK, Albeck H, Hansen JPH, et al. Epstein-Barr virus in nasopharyngeal and salivary carcinomas of Greenland Eskimos. *Br J Cancer* 1982; 46(5):721–728.
24. Krishnamurthy S, Lanier AP, Dohan P, et al. Salivary gland cancer in Alaskan natives, 1966–1980. *Hum Pathol* 1987; 18(10):986–996.
25. Huang DP, Ng HK, Ho YH, et al. Epstein-Barr virus (EBV)-associated undifferentiated carcinoma of the parotid gland. *Histopathology* 1988; 13(5):509–517.
26. Sheen TS, Tsai CC, Ko JY, et al. Undifferentiated carcinoma of the major salivary glands. *Cancer* 1997; 80(3):357–363.
27. Merrick Y, Albeck H, Nielsen NH, et al. Familial clustering of salivary gland carcinoma in Greenland. *Cancer* 1986; 57(10):2097–2102.
28. Autio-Harminen H, Pääkkö P, Alavaikko M, et al. Familial occurrence of malignant lymphoepithelial lesion of the parotid in a Finnish family with dominantly inherited trichoepithelioma. *Cancer* 1988; 61(1):161–166.
29. Hamilton-Dutoit SJ, Therkildsen MH, Nielsen NH, et al. Undifferentiated carcinoma of the salivary gland in Greenlandic Eskimos: demonstration of Epstein-Barr virus DNA by *in situ* nucleic acid hybridization. *Hum Pathol* 1991; 22(8):811–815.
30. Kotsianti A, Costopoulos J, Morgello S, et al. Undifferentiated carcinoma of the parotid gland in a white patient: detection of Epstein-Barr virus by *in situ* hybridization. *Hum Pathol* 1996; 27(1):87–90.
31. Sehested M, Hainau B, Albeck H, et al. Ultrastructural investigation of anaplastic salivary gland carcinoma in Eskimos. *Cancer* 1985; 55(11):2732–2736.
32. Jen KY, Cheng J, Li J, et al. Mutational events in LMP1 gene of Epstein-Barr virus in salivary gland lymphoepithelial carcinomas. *Int J Cancer* 2003; 105(5):654–660.
33. Ma J, Chan JK, Chow CW, et al. Lymphadenoma: a report of three cases of an uncommon salivary gland neoplasm. *Histopathology* 2002; 41(4):342–350.
8. Garrido A, Humphrey G, Squire RS, et al. Sialoblastoma. *Br J Plast Surg* 2000; 53(8):697–699.
9. Green RS, Tunkel DE, Small D, et al. Sialoblastoma: association with cutaneous hamartoma (organoid nevus)? *Pediatr Dev Pathol* 2000; 3(5):504–505.
10. Harris MD, McKeever P, Robertson JM. Congenital tumours of the salivary gland: a case report and review. *Histopathology* 1990; 17(2):155–157.
11. Hsueh C, Gonzalez-Crussi F. Sialoblastoma: a case report and review of the literature on congenital epithelial tumors of salivary gland origin. *Pediatr Pathol* 1992; 12(2): 205–214.
12. Huang R, Jaffer S. Imprint cytology of metastatic sialoblastoma. A case report. *Acta Cytol* 2003; 47(6):1123–1126.
13. Luna MA. Sialoblastoma and epithelial tumors in children: their morphologic spectrum and distribution by age. *Adv Anat Pathol* 1999; 6(5):287–292.
14. Mostafapour SP, Folz B, Barlow D, et al. Sialoblastoma of the submandibular gland: report of a case and review of the literature. *Int J Pediatr Otorhinolaryngol* 2000; 53(2): 157–161.
15. Ortiz-Hidalgo C, de Leon-Bojorge B, Fernandez-Sobrinho G, et al. Sialoblastoma: report of a congenital case with dysembryogenic alterations of the adjacent parotid gland. *Histopathology* 2001; 38(1):79–80.
16. Ozdemir I, Simsek E, Silan F, et al. Congenital sialoblastoma (embryoma) associated with premature centromere division and high level of alpha-fetoprotein. *Prenat Diagn* 2005; 25(8):687–689.
17. Roth A, Micheau C. Embryoma (or embryonal tumor) of the parotid gland: report of two cases. *Pediatr Pathol* 1986; 5(1):9–15.
18. Seifert G, Donath K. The congenital basal cell adenoma of salivary glands. Contribution to the differential diagnosis of congenital salivary gland tumours. *Virchows Arch* 1997; 430(4):311–319.
19. Siddiqi SH, Solomon MP, Haller JO. Sialoblastoma and hepatoblastoma in a neonate. *Pediatr Radiol* 2000; 30(5):349–351.
20. Simpson PR, Rutledge JC, Schaefer SD, et al. Congenital hybrid basal cell adenoma–adenoid cystic carcinoma of the salivary gland. *Pediatr Pathol* 1986; 6(2–3):199–208.
21. Tatlidede S, Karsidag S, Ugurlu K, et al. Sialoblastoma: a congenital epithelial tumor of the salivary gland. *J Pediatr Surg* 2006; 41(7):1322–1325.
22. Verret DJ, Galindo RL, DeFatta RJ, et al. Sialoblastoma: a rare submandibular gland neoplasm. *Ear Nose Throat J* 2006; 85(7):440–442.
23. Williams SB, Ellis GL, Warnock GR. Sialoblastoma: a clinicopathologic and immunohistochemical study of 7 cases. *Ann Diagn Pathol* 2006; 10(6):320–326.
24. Yekeler E, Dursun M, Gun F, et al. Sialoblastoma: MRI findings. *Pediatr Radiol* 2004; 34(12):1005–1007.
25. Shet T, Ramadwar M, Sharma S. An eyelid sialoblastoma like tumor with a sarcomatoid myoepithelial component. *Pediatr Dev Pathol* 2007; 10(4):309–314.
26. Ellis GL, Auclair PL. Sialoblastoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:136–142.
27. Scott JX, Krishnan S, Bourne AJ, et al. Treatment of metastatic sialoblastoma with chemotherapy and surgery. *Pediatr Blood Cancer* 2008; 50(1):134–137.

Sialoblastoma

1. Brandwein-Gensler MS. Sialoblastoma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:253.
2. Vawter GF, Tefft M. Congenital tumors of the parotid gland. *Arch Pathol* 1966; 82(3):242–245.
3. Taylor GP. Congenital epithelial tumor of the parotid-sialoblastoma. *Pediatr Pathol* 1988; 8(4):447–452.
4. Adkins GF. Low grade basaloid adenocarcinoma of salivary gland in childhood—the so-called hybrid basal cell adenoma–adenoid cystic carcinoma. *Pathology* 1990; 22(4): 187–190.
5. Batsakis JG, Frankenthaler R. Embryoma (sialoblastoma) of salivary glands. *Ann Otol Rhinol Laryngol* 1992; 101(11): 958–960.
6. Alvarez-Mendoza A, Calderon-Elvir C, Carrasco-Daza D. Diagnostic and therapeutic approach to sialoblastoma: report of a case. *J Pediatr Surg* 1999; 34(12):1875–1877.
7. Brandwein M, Al-Naeif NS, Manwani D, et al. Sialoblastoma: clinicopathological/immunohistochemical study. *Am J Surg Pathol* 1999; 23(3):342–348.

Hybrid Tumors

1. Seifert G, Donath K. Hybrid tumors of salivary glands: definition and classification of five rare cases. *Eur J Cancer B Oral Oncol* 1996; 32B(4):251–259.

2. Gnepp DR, Brandwein MS, Henley JD. Hybrid tumors. In: Gnepp DR, eds. *Surgical Pathology of the Head and Neck*. Philadelphia: WB Saunders, 2001:406–407.
3. Grenko RT, Abendroth CS, Davis AT, et al. Hybrid tumors or salivary gland tumors sharing common differentiation pathways? Reexamining adenoid cystic and epithelial-myoepithelial carcinomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86(2):188–195.
4. Croitoru CM, Suarez PA, Luna MA. Hybrid carcinomas of salivary glands: report of 4 cases and review of the literature. *Arch Pathol Lab Med* 1999; 123(8):698–702.
5. Chetty R, Medley P, Essa A. Hybrid carcinomas of salivary glands. *Arch Pathol Lab Med* 2000; 124(4):494–496.
6. Nagao T, Sugano I, Ishida Y, et al. Hybrid carcinomas of the salivary glands: report of nine cases with a clinicopathologic, immunohistochemical, and *p53* gene alteration analysis. *Mod Pathol* 2002; 15(7):724–733.
7. Ballestin C, Lopez-Carreira M, Lopez JI. Combined acinic cell mucoepidermoid carcinoma of the parotid gland: report of a case with immunohistochemical study. *APMIS* 1996; 104(2):99–102.
8. Kamio N, Tanaka Y, Mukai M, et al. A hybrid carcinoma: adenoid cystic carcinoma and salivary duct carcinoma of the salivary gland: an immunohistochemical study. *Virchows Arch* 1997; 430(6):495–500.
9. Simpson PR. Pitfalls in salivary gland pathology: hybrid epithelial myoepithelial carcinoma and adenoid cystic carcinoma [abst 067]. *Pathol Res Pract* 1997; 193:342.
10. Snyder ML, Paulino AF. Hybrid carcinoma of the salivary gland: salivary duct adenocarcinoma adenoid cystic carcinoma. *Histopathology* 1999; 35(4):380–383.
11. Zardawi IM. Hybrid carcinoma of the salivary gland. *Histopathology* 2000; 37(3):283–284.
12. Ruiz-Godoy LM, Mosqueda-Taylor A, Suarez-Roa L, et al. Hybrid tumours of the salivary glands. A report of two cases involving the palate and a review of the literature. *Eur Arch Otorhinolaryngol* 2003; 260(6):312–315.
13. Murphy JG, Lonsdale R, Premachandra D, et al. Salivary hybrid tumour: adenoid cystic carcinoma and basal cell adenocarcinoma. *Virchows Arch* 2006; 448(2):236–238.
14. Seifert G, Donath K. Multiple tumours of the salivary glands: terminology and nomenclature. *Eur J Cancer B Oral Oncol* 1996; 32B(1):3–7.
15. Gnepp DR, Schroeder W, Heffner D. Synchronous tumors arising in a single major salivary gland. *Cancer* 1989; 63(6):1219–1224.
16. Brandwein MS, Jagirdar J, Patil J, et al. Salivary duct carcinoma (cribriform salivary carcinoma of excretory ducts). A clinicopathologic and immunohistochemical study of 12 cases. *Cancer* 1990; 65(10):2307–2314.
17. Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. *Am J Surg Pathol* 2007; 31(1):44–57.
18. Shinozaki A, Nagao T, Endo H, et al. Sebaceous epithelial-myoepithelial carcinoma of the salivary gland: clinicopathologic and immunohistochemical analysis of six cases of a new histologic variant. *Am J Surg Pathol* 2008; 32(6):913–923.
19. Stanley RJ, Weiland LH, Olsen KD, et al. Dedifferentiated acinic cell (acinous) carcinoma of the parotid gland. *Otolaryngol Head Neck Surg* 1988; 98(2):155–161.
20. Cheuk W, Chan JK, Ngan RK. Dedifferentiation in adenoid cystic carcinoma of salivary gland: an uncommon complication associated with an accelerated clinical course. *Am J Surg Pathol* 1999; 23(4):465–472.
21. Nagao T, Gaffey TA, Serizawa H, et al. Dedifferentiated adenoid cystic carcinoma: a clinicopathologic study of 6 cases. *Mod Pathol* 2003; 16(12):1265–1272.
22. Seethala RR, Hunt JL, Baloch ZW, et al. Adenoid cystic carcinoma with high-grade transformation: a report of 11 cases and a review of the literature. *Am J Surg Pathol* 2007; 31(11):1683–1694.
23. Alos L, Carrillo R, Ramos J, et al. High-grade carcinoma component in epithelial-myoepithelial carcinoma of salivary glands clinicopathological, immunohistochemical and flow-cytometric study of three cases. *Virchows Arch* 1999; 434(4):291–299.
24. Pelkey TJ, Mills SE. Histologic transformation of polymorphous low-grade adenocarcinoma of salivary gland. *Am J Clin Pathol* 1999; 111(6):785–791.
25. Simpson RH, Pereira EM, Ribeiro AC, et al. Polymorphous low-grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. *Histopathology* 2002; 41(3):250–259.

Intraosseous (Central) Salivary Gland Tumors

1. Brookstone MS, Huvos AG. Central salivary gland tumors of the maxilla and mandible: a clinicopathologic study of 11 cases with an analysis of the literature. *J Oral Maxillofac Surg* 1992; 50(3):229–236.
2. Waldron CA, Koh ML. Central mucoepidermoid carcinoma of the jaws: report of four cases with analysis of the literature and discussion of the relationship to mucoepidermoid, sialodontogenic, and glandular odontogenic cysts. *J Oral Maxillofac Surg* 1990; 48(8):871–877.
3. Ellis GL, Auclair PL. Central mucoepidermoid carcinoma. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington, DC: Armed Forces Institute of Pathology, 1996:172–175.
4. Bouquot JE, Gnepp DR, Dardick I, et al. Intraosseous salivary tissue: jawbone examples of choristomas, hamartomas, embryonic rests and inflammatory entrapment. Another histogenetic source for intraosseous adenocarcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90(2):205–217.
5. Capodiferro S, Scully C, Macaita MG, et al. Bilateral intraosseous adenoid cystic carcinoma of the mandible: report of a case with lung metastases at first clinical presentation. *Oral Dis* 2005; 11(2):109–112.
6. Chen YK, Chen CH, Lin CC, et al. Central adenoid cystic carcinoma of the mandible manifesting as an endodontic lesion. *Int Endod J* 2004; 37(10):711–716.
7. Favia G, Maiorano E, Orsini G, et al. Central (intraosseous) adenoid cystic carcinoma of the mandible: report of a case with periapical involvement. *J Endod* 2000; 26(12):760–763.
8. Al-Sukhun J, Lindqvist C, Hietanen J, et al. Central adenoid cystic carcinoma of the mandible: case report and literature review of 16 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 101(3):304–308.
9. Berho M, Huvos AG. Central hyalinizing clear cell carcinoma of the mandible and the maxilla: a clinicopathologic study of two cases with an analysis of the literature. *Hum Pathol* 1999; 30(1):101–105.
10. Martinez-Madrigal F, Pineda-Daboin K, Casiraghi O, et al. Salivary gland tumors of the mandible. *Ann Diagn Pathol* 2000; 4(6):347–353.
11. Kikuchi Y, Hirota M, Iwai T, et al. Salivary duct carcinoma in the mandible: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103(3):e41–e46.
12. Ojha J, Bhattacharyya I, Islam MN, et al. Intraosseous pleomorphic adenoma of the mandible: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(2):e21–e26.
13. Cuesta Gil M, Bucci T, Navarro Cuellar C, et al. Intraosseous myoepithelioma of the maxilla: clinicopathologic

features and therapeutic considerations. *J Oral Maxillofac Surg* 2008; 66(4):800–803.

14. Pires FR, Chen SY, da Cruz Perez DE, et al. Cytokeratin expression in central mucoepidermoid carcinoma and glandular odontogenic cyst. *Oral Oncol* 2004; 40(1):545–551.
 15. Shen J, Fan M, Chen X, et al. Glandular odontogenic cyst in China: report of 12 cases and immunohistochemical study. *J Oral Pathol Med* 2006; 35(3):175–182.
- Soft Tissue Tumors*
1. Seifert G, Oehne H. Mesenchymal (non-epithelial) salivary gland tumors. Analysis of 167 tumor cases of the salivary gland register. *Laryngol Rhinol Otol (Stuttg)* 1986; 65(9):485–491.
 2. McDaniel RK. Benign mesenchymal neoplasms. In Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:489–513.
 3. Auclair PL, Ellis GL. Nonlymphoid sarcomas of the major salivary glands. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:514–527.
 4. Ellis GL, Auclair PL. Nonlymphoid mesenchymal neoplasms. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:375–385.
 5. Gnepp DR. Soft tissue tumours. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:275.
 6. Auclair PL, Langloss JM, Weiss SW, et al. Sarcomas and sarcomatoid neoplasms of the major salivary gland regions. A clinicopathologic and immunohistochemical study of 67 cases and review of the literature. *Cancer* 1986; 58(6):1305–1315.
 7. Cho KJ, Ro JY, Choi J, et al. Mesenchymal neoplasms of the major salivary glands: clinicopathological features of 18 cases. *Eur Arch Otorhinolaryngol* 2007, in press.
 8. Nagao K, Matsuzaki O, Shigematsu H, et al. Histopathologic studies of benign infantile hemangioendothelioma of the parotid gland. *Cancer* 1980; 46(10):2250–2256.
 9. Odell E. Haemangioma. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press 2005; 276.
 10. Childers EL, Furlong MA, Fanburg-Smith JC. Hemangioma of the salivary gland. A study of ten cases of a rarely biopsied/excised lesion. *Ann Diagn Pathol* 2002; 6(6):339–344.
 11. Ferreiro JA, Nascimento AG. Solitary fibrous tumour of the major salivary glands. *Histopathology* 1996; 28(3):261–264.
 12. Ogawa I, Sato S, Kudo Y, et al. Solitary fibrous tumor with malignant potential arising in sublingual gland. *Pathol Int* 2003; 53(1):40–45.
 13. Williams SB, Foss RD, Ellis GL. Inflammatory pseudotumors of the major salivary glands. Clinicopathologic and immunohistochemical analysis of six cases. *Am J Surg Pathol* 1992; 16(9):896–902.
 14. Van Weert S, Manni JJ, Driessen A. Inflammatory myofibroblastic tumor of the parotid gland: case report and review of the literature. *Acta Otolaryngol* 2005; 125(4):433–437.
 15. Kojima M, Nakamura S, Itoh H, et al. Inflammatory pseudotumor of the submandibular gland: report of a case presenting with autoimmune disease-like clinical manifestations. *Arch Pathol Lab Med* 2001; 125(8):1095–1097.
 16. Walts AE, Perzik SL. Lipomatous lesions of the parotid area. *Arch Otolaryngol* 1976; 102(4):230–232.
 17. Baker SE, Jensen JL, Correll RW. Lipomas of the parotid gland. *Oral Surg Oral Med Oral Pathol* 1981; 52(2):167–171.
 18. Fregnani ER, Pires FR, Falzoni R, et al. Lipomas of the oral cavity. Clinical findings, histological classification and proliferative activity of 46 cases. *Int J Oral Maxillofac Surg* 2003; 32(1):49–53.
 19. Nagao T, Sugano I, Ishida Y, et al. Sialolipoma: a report of seven cases of a new variant of salivary gland lipoma. *Histopathology* 2001; 38(1):30–36.
 20. Fanburg-Smith JC, Furlong MA, Childers EL. Oral and salivary gland angiosarcoma. A clinicopathologic study of 29 cases. *Mod Pathol* 2003; 16(3):263–271.
 21. Castle JT, Thompson LD. Kaposi sarcoma of major salivary gland origin. A clinicopathologic series of six cases. *Cancer* 2000; 88(1):15–23.
 22. Fanburg-Smith JC, Furlong MA, Childers EL. Liposarcoma of the oral and salivary gland region. A clinicopathologic study of 18 cases with emphasis on specific sites, morphologic subtypes, and clinical outcome. *Mod Pathol* 2002; 15(10):1020–1031.
 23. Tse LL, Finkelstein SD, Siegler RW, et al. Osteoclast-type giant cell neoplasm of salivary gland. A microdissection-based comparative genotyping assay and literature review: extraskeletal “giant cell tumor of bone” or osteoclast-type giant cell “carcinoma”? *Am J Surg Pathol* 2004; 28(7):953–961.
 24. Kadivar M, Nilipour Y, Sadeghipour A. Osteoclast-like giant-cell tumor of the parotid with salivary duct carcinoma: case report and cytologic, histologic, and immunohistochemical findings. *Ear Nose Throat J* 2007; 86(10):628–630.
 25. Luna MA, Tortoledo ME, Ordóñez NG, et al. Primary sarcomas of the major salivary glands. *Arch Otolaryngol Head Neck Surg* 1991; 117(3):302–306.
 26. Drut R, Altamirano E. Endothelial cells of intramuscular (infantile) hemangioma express glut1. *Int J Surg Pathol* 2007; 15(2):166–168.
 27. Hornigold R, Morgan PR, Pearce A, et al. Congenital sialolipoma of the parotid gland first reported case and review of the literature. *Int J Pediatr Otorhinolaryngol* 2005; 69(3):429–434.
 28. Ramer N, Lumerman HS, Ramer Y. Sialolipoma: report of two cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104(6):809–813.
 29. Bansal B, Ramavat AS, Gupta S, et al. Congenital sialolipoma of parotid gland: a report of rare and recently described entity with review of literature. *Pediatr Dev Pathol* 2007; 10(3):244–246.
 30. Yau KC, Tsang WY, Chan JK. Lipoadenoma of the parotid gland with probable striated duct differentiation. *Mod Pathol* 1997; 10(3):242–246.
 31. Hirokawa M, Shimizu M, Manabe T, et al. Oncocytic lipoadenoma of the submandibular gland. *Hum Pathol* 1998; 29(4):410–412.
 32. Seifert G, Donath K, Schafer R. Lipomatous pleomorphic adenoma of the parotid gland: classification of lipomatous tissue in salivary glands. *Pathol Res Pract* 1999; 195(4):247–252.
- Malignant Lymphomas*
1. Colby TV, Dorfman RF. Malignant lymphomas involving the salivary glands. *Pathol Annu* 1979; 14(pt 2):307–324.
 2. Gleeson MJ, Bennett MH, Cawson RA. Lymphomas of salivary glands. *Cancer* 1986; 58(3):699–704.
 3. Ellis GL, Auclair PL. Malignant lymphomas of the major salivary glands. In: *Atlas of Tumor Pathology: Tumors of the Salivary Glands*. 3rd series, fascicle 17. Washington DC: Armed Forces Institute of Pathology, 1996:387–402.
 4. Barnes L, Myers EN, Prokopakis EP. Primary malignant lymphoma of the parotid gland. *Arch Otolaryngol Head Neck Surg* 1998; 124(5):573–577.

5. Chan ACL, Chan JKC, Abbondanzo SL. Haematolymphoid tumours. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:277–280.
6. Chan JK, Tsang WY, Hui PK, et al. T- and T/natural killer-cell lymphomas of the salivary gland: a clinicopathologic, immunohistochemical and molecular study of six cases. *Hum Pathol* 1997; 28(2):238–246.
7. Harris NL. Lymphoid proliferations of the salivary glands. *Am J Clin Pathol* 1999; 111(suppl 1):S94–S103.
8. Hyjek E, Smith WJ, Isaacson PG. Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialoadenitis. *Hum Pathol* 1988; 19(7):766–776.
9. Abbondanzo SL. Extranodal marginal-zone B-cell lymphoma of the salivary gland. *Ann Diagn Pathol* 2001; 5(4):246–254.
10. Jaffe ES. Lymphoid lesions of the head and neck: a model of lymphocyte homing and lymphomagenesis. *Mod Pathol* 2002; 15(3):255–263.
11. Ambosetti A, Zanotti R, Pattaro C, et al. Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjogren's syndrome or hepatitis C virus infection. *Br J Hematol* 2004; 126(1):43–49.
12. Park CK, Manning JT Jr., Battifora H, et al. Follicle center lymphoma and Warthin tumor involving the same anatomic site. Report of two cases and review of the literature. *Am J Clin Pathol* 2000; 113(1):113–119.
13. Harris NL, Jaffe ES, Stein H, et al. *World Health Organization Classification of Tumours. Pathology and Genetics of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, 2001.
14. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer* 1983; 52(8):1410–1416.
15. Isaacson PG. Mucosa-associated lymphoid tissue lymphoma. *Semin Hematol* 1999; 36(2):139–147.
16. Du M, Diss TC, Xu C, et al. Ongoing mutation on MALT lymphoma immunoglobulin gene suggests that antigen stimulation plays a role in clonal expansion. *Leukemia* 1996; 10(7):1190–1197.
17. Bahler DW, Swerdlow SH. Clonal salivary gland infiltrates associated with myoepithelial sialadenitis (Sjogren's syndrome) begin as nonmalignant antigen-selected expansions. *Blood* 1998; 91(6):1864–1872.
18. Diss TC, Wotherspoon AC, Speight P, et al. B-cell monoclonality, Epstein-Barr virus and t(14;18) in myoepithelial sialadenitis and low grade B-cell MALT lymphoma of the parotid gland. *Am J Surg Pathol* 1995; 19(5):531–539.
19. Quintana PG, Kapadia SB, Bahler DW, et al. Salivary gland lymphoid infiltrates associated with lymphoepithelial lesions. A clinicopathologic, immunophenotypic, and genotypic study. *Hum Pathol* 1997; 28(7):850–861.
20. Harris NL, Isaacson PG. What are the criteria for distinguishing MALT from non-MALT lymphoma at extranodal sites? *Am J Clin Pathol* 1999; 111(suppl 1):S126–S132.
21. Casato M, Agnello V, Pucillo LP, et al. Predictors of long-term response to high-dose interferon therapy in type II cryoglobulinemia associated with hepatitis C virus infection. *Blood* 1997; 90(10):3865–3873.
22. Dierlamm J, Wlodarska I, Michaux L, et al. Genetic abnormalities in marginal zone lymphomas. *Hematol Oncol* 2000; 18(1):1–9.
23. Remstein ED, James CD, Kurtin PJ. Incidence and subtype of Api2-MALT1 fusion translocations in extranodal, nodal and splenic marginal zone lymphomas. *Am J Pathol* 2000; 156(4):1183–1190.
24. Liu H, Ye H, Dogan A, et al. T(11;18)(q21;q21) is associated with advanced mucosa associated lymphoid tissue lymphoma that expresses nuclear BCL-10. *Blood* 2001; 98(4):1182–1187.
25. Streubel B, Lamprecht A, Dierlamm J, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood* 2003; 101(6):2335–2339.
26. Streubel B, Simonitsch-Klupp I, Mullauer L, et al. Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. *Leukemia* 2004; 18(10):1722–1726.
27. Streubel B, Vinatzer U, Lamprecht A, et al. T(3;14)(p14.1;q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. *Leukemia* 2005; 19(4):652–658.
28. Bacon CM, Du MQ, Dogan A. Mucosa-associated lymphoid tissue (MALT) lymphoma: a practical guide for pathologists. *J Clin Pathol* 2007; 60(4):361–372.

Secondary Tumors

1. Lönning T, Jäkel KT. Secondary tumours. In: Barnes L, Eveson JW, Reichart P, et al., eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press, 2005:281.
2. Gnepp DR. Metastatic disease to the major salivary glands. In: Ellis GL, Auclair PL, Gnepp DR, eds. *Surgical Pathology of the Salivary Glands*. Philadelphia: WB Saunders, 1991:560–569.
3. Ying YL, Johnson JT, Myers EN. Squamous cell carcinoma of the parotid gland. *Head Neck* 2006; 28(7):626–632.
4. Seifert G, Hennings K, Caselitz J. Metastatic tumors to the parotid and submandibular glands—analysis and differential diagnosis of 108 cases. *Pathol Res Pract* 1986; 181(6):684–692.
5. Auclair PL. Tumor-associated lymphoid proliferation in the parotid gland. A potential diagnostic pitfall. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):19–26.
6. Conley J, Arena S. Parotid gland as a focus of metastasis. *Arch Surg* 1963; 87:757–764.
7. Rees R, Maples M, Lynch JB, et al. Malignant secondary parotid tumors. *South Med J* 1981; 74(9):1050–1052.
8. Nuyens M, Schüpbach J, Stauffer E, et al. Metastatic disease to the parotid gland. *Otolaryngol Head Neck Surg* 2006; 135(6):844–848.

Index

- AAD. *See* Acroangiodermatitis (AAD)
ABC. *See* Aneurysmal bone cyst (ABC)
ABCD. *See* Anterior buccal cortical defect (ABCD)
AC. *See* Atypical carcinoid (AC)
Acanthamoeba keratitis, 1571–1572
Acantholytic actinic keratosis (AK), 1491
Acantholytic squamous cell carcinoma (ALSCC), 159–160
 clinical features, 160
 diagnosis, 160
 etiology, 159–160
 overviews, 159
 pathology, 160
 treatment, 160
Acanthosis, 253
ACC. *See* Adenoid cystic carcinomas (ACC)
Accessory tragi, 425–426
Acinar cells, 20, 27
Acinic cell carcinomas, 29–30, 390, 542–546
Acne keloidalis, 1342
Acoustic neuromas, 454–455, 691–692
Acquired cholesteatomas, 436–437
Acquired encephalocele, 440
Acquired melanosis, 1560–1561
Acquired nonneoplastic lesions, 427–432
 cholesterol granulomas, 430
 inflammatory otic polyps, 431
 malakoplakia, 431–432
 necrotizing malignant external otitis (NEO), 427–428
 otitis media, 428–429
 tympanosclerosis, 429–430
Acroangiodermatitis (AAD), 1522
Actinic cheilitis, 279–280
 clinical features, 279
 defined, 279
 diagnosis, 280
 pathology, 280
 treatment, 280
Actinic keratosis (AK)
 clinical features, 1489–1490
 differential diagnosis, 1490–1491
 histologic features, 1490
 imaging studies, 1490
 immunohistochemical studies, 1490
 treatment and prognosis, 1491
Actinomyces, 1621
Actinomyces spp, 953, 1013
Actinomycoses
 clinical background, 1620–1621
 etiology, 1621
 histopathology, 1621
 treatment, 1621
Acute bacterial rhinosinusitis, 345
Acute bacterial sinusitis, 345
Acute exacerbation of chronic sinusitis (AECS), 1609
Acute myeloid leukemia, 1355
Acute necrotizing ulcerative gingivitis (ANUG), 259
Acute suppurative osteomyelitis
 pathologic features, 958–959
 radiologic features, 958
Acute suppurative sialadenitis, 484–485
Acute thyroiditis, 4, 1391–1392
Acyclovir, 1673
Addison's disease, 1460
Adenocarcinoma, 578–580
 of left supraclavicular lymph node, 1151
Adenocarcinomas
 ceruminous gland, 462–463
 intestinal-type, 383–387
 middle ear, 466–467
 of nasal cavity/paranasal sinuses, classification, 383
 nonintestinal-type, 387–389
Adenoid cystic carcinomas (ACC), 23, 24–25, 76, 168–169, 178, 390, 552–557
Adenoid hyperplasia, 225–226
 pathology, 226
 treatment, 226
Adenoid squamous carcinomas, 313–314
Adenomatoid nodules. *See* Hyperplastic nodules
Adenomatoid odontogenic tumor (AOT)
 AMBN mutation, 1240
 differential diagnosis, 1240
 electron microscopy of, 1239–1240
 imaging, 1236–1237
 immunohistochemistry, 1238–1239
 pathology and pathogenesis, 1238
 patterns of, 1237
 prevalence and incidence, 1235–1236
 treatment and prognosis, 1240
Adenosine triphosphate-binding cassette transporter A1 (ABCA1), 1730
Adenosquamous carcinomas, 158–159, 312–313
 clinical features, 158
 diagnosis, 159
 etiology, 158
 immunohistochemistry, 159
 overviews, 158
 pathology, 158–159
 treatment, 159
Adipose tissue, 20
Adult onset laryngeal papillomas, 1677
Adult T-cell leukemia/lymphoma, 1072
AFD. *See* Ameloblastic fibro-dentinoma (AFD)
AFIP. *See* Armed Forces Institute of Pathology (AFIP)
Afipia felis, 1011
AFOD. *See* Ameloblastic fibro-odontoma (AFOD)
Aggressive osteoblastoma, 970
AIDS, 50
AIDS-related lymphomas, 1667
AIDS-related nasopharyngeal lesions, 1661
AIDS-related parotid cysts (ARPC), 1660–1661
AIDS toxoplasmosis, 1688
AIF. *See* Apoptosis inducing factor (AIF) and apoptotic cell death
AJCC. *See* American Joint Committee on Cancer (AJCC)
AJCC 2002 melanoma staging, 1508
AK. *See* Actinic keratosis (AK)
Albendazole, 1690
Albright's hereditary osteodystrophy, 1460
ALCD. *See* Anterior lingual cortical defect (ALCD)
ALCL. *See* Anaplastic large cell lymphoma (ALCL)
Alcohol, oral cancer, 288
ALHE. *See* Angiolymphoid hyperplasia with eosinophilia (ALHE)
ALK+ anaplastic large cell lymphoma, 1065–1068
 clinical features, 1066
 differential diagnosis, 1068
 immunohistochemistry, 1066–1067
 molecular genetic data, 1067–1068
 pathology, 1066
ALK- anaplastic large cell lymphoma, 1068
ALK+ DLBCL, 1042
ALK gene, 1042
Allergic fungal rhinosinusitis (AFRS), 354–356
 clinical features, 355
 etiology, 355
 pathology, 355–356
 treatment, 356
Allergic fungal sinusitis (eosinophilic mucin rhinosinusitis)
 clinical presentation, 1633
 etiology, 1633
 histopathology, 1633–1634
 treatment, 1634
Allergic granulomatosis and vasculitis (AGV). *See* Churg-Strauss syndrome
Allergic mucus, 354–356
Allergic rhinosinusitis, 343–345
Alopecia, 252
ALSCC. *See* Acantholytic squamous cell carcinoma (ALSCC)
Alternaria, 1640
Alveolar cysts, 1343
Alveolar mucosa, squamous cell carcinomas of, 298–300
Alveolar RMS (ARMS), 869, 872–873
Alveolar soft part sarcoma (ASPS), 901–904, 1363
 in children, 1346
Amalgam tattoo, 204–205
 clinical features, 205
 pathology, 205
 treatment, 205
AMCA. *See* Ameloblastic carcinoma (AMCA)
Ameloblastic carcinoma (AMCA), 1292
 differential diagnosis, 1295
 DNA microarray study, 1295
 etiology of, 1293–1294
 frequency of, 1293
 gender ratio, 1293
 growth rate, 1293
 immunohistochemistry, 1294
 locations of, 1293
 ultrastructure of, 1294
Ameloblastic fibro-dentinoma (AFD)
 clinical features, 1247
 immunohistochemistry
 neural tissue markers, 1248
 pathogenesis of, 1247–1248
 treatment and prognosis, 1248
 ultrastructure of, 1248

- Ameloblastic fibroma (AMF)
 clinical features, 1241–1242
 differential diagnosis, 1245–1246
 etiology of, 1242–1244
 imaging of, 1242
 immunohistochemistry, 1244
 molecular-genetic data, 1245
 treatment and prognosis, 1246–1247
 ultrastructure of, 1245
- Ameloblastic fibro-odontoma (AFOD)
 clinical features, 1248–1249
 differential diagnosis, 1252
 etiology of, 1249–1250
 immunohistochemistry
 CK in epithelial component of, 1250
 enamel proteins in, 1251
 growth factors, 1251
 MIB-1 antibody, 1251
 nestin and vimentin, 1251
 molecular-genetic data, 1252
 osteocalcin transcripts and, 1252
 radiographs, 1249
 treatment and prognosis, 1252
 ultrastructure of, 1251–1252
- Ameloblastomas, 69
 ameloblastin (AMBN) gene mutations in, 1213
 amelogenin and, 1213
 differential diagnosis, 1214
 molecules involved in progression of
 angiogenic factors, 1214
 cell adhesion molecules, 1213
 matrix-degrading proteinases, 1213–1214
 osteolytic cytokines, 1214
 treatment and prognosis, 1214–1215
 tumorigenesis and/or cell differentiation,
 molecules involved in
 apoptosis-related factors, 1212
 cell cycle-related factors, 1212
 DNA-repair genes, 1211
 gene modifications and, 1210–1211
 growth factors, 1211–1212
 hard tissue-related proteins, 1213
 oncogenes, 1210
 oncoviruses, 1211
 telomerase activity, 1212
 tooth development, regulators of, 1213
 tumor suppressor genes, 1211
- Amelogenin and calcifying odontogenic cyst (COC), 1265
- American College of Rheumatology, 253, 652
- American Joint Committee on Cancer (AJCC), 863
 staging of nasopharyngeal carcinomas, 396
 staging of vestibular carcinomas, 373
- AMF. *See* Ameloblastic fibroma (AMF)
- 5-aminolevulinic acid, 1488
- Amiodarone drugs, 1386
- Amphotericin B, 1631, 1637, 1652
- Ampicillin-sulbactam, 1611
- Amputation neuroma. *See* Traumatic neuroma
- Amyloid, 14
- Amyloid goiter, 1391
- Amyloidosis, 484, 1027–1029
 classification, 1028
 clinical features, 1028–1029
 pathology, 1029
- ANA. *See* Antinuclear antibodies (ANA)
- Anaplastic carcinoma, 14–15
 clinical features, 1407
 molecular genetics, 1408–1409
 pathology, 1408
 treatment and prognosis, 1409
- Anaplastic large cell lymphoma (ALCL), 42–43
 ALK+, 1065–1068
 ALK-, 1068
- ANCA. *See* Antineutrophil cytoplasmic autoantibodies (ANCA)
- ANCA titers. *See* Antineutrophil cytoplasmic antibodies (ANCA) titers
- Ancillary studies, of lymph nodes, 39–40
 cell block, 39
 core needle biopsy, 39
 FISH studies, 40
 flow cytometry, 39–40
 PCR studies, 40
- Androgen receptor (AR), 31
- Aneuploidy, 713
- Aneurysmal bone cyst (ABC), 963, 986–987
- Angiofibroma
 clinical features, 834
 differential diagnosis, 836
 electron microscopy, 836
 imaging, 834–835
 immunohistochemistry, 836
 molecular-genetic data, 836
 pathology, 835–836
 treatment and prognosis, 836–837
- Angiofibromas, 64
- Angioimmunoblastic T-cell lymphoma, 1064
- Angiolymphoid hyperplasia with eosinophilia (ALHE)
 clinical features, 1528
 defined, 1528
 differential diagnosis, 1529
 electron microscopy, 1529
 imaging studies, 1528
 immunohistochemistry, 1529
 molecular genetics, 1529
 pathology, 1528
 treatment and prognosis, 1529
- Angiomatoid fibrous histiocytoma (AFH).
See Malignant fibrous histiocytoma
- Angiosarcoma, 867–869, 982–983, 1415–1416
- Angle recession, 1584
- Annexin V activity and apoptotic cells
 detection, 1212
- Anterior buccal cortical defect (ABCD), 963
- Anterior lingual cortical defect (ALCD), 963
- Anthelmintics, 1690
- Anthraxis, 1444
- Antibiotics, 260
- Anticonvulsants drugs, 260
- Antifungal therapy, 257
- Antigen, 249
- Antimalarial drugs, 254
- Antimicrobial therapy, 37
- Antineutrophil cytoplasmic antibodies (ANCA) titers, 441
- Antineutrophil cytoplasmic antibodies / autoantibodies (ANCA), 649, 650
 cytoplasmic (C-ANCA), 650
 perinuclear (P-ANCA), 650
- Antineutrophil cytoplasmic autoantibodies (ANCA)
 in Wegener's granulomatosis, 443–444
- Antinuclear antibodies (ANA), 252
- Anti-PTH immunohistochemistry, 1434
- Antoni type A, 679
- Antrochoanal polyps (ACP), 350–351
- ANUG. *See* Acute necrotizing ulcerative gingivitis (ANUG)
- AOT. *See* Adenomatoid odontogenic tumor (AOT)
- APAF-1. *See* Apoptotic protease activating factor-1 (APAF-1) and apoptotic cell death
- Aplasia, of salivary glands, 476–477
- Aplasia cutis congenital (ACC), 1537
- Apocrine hidrocystomas, 1484
- Apoptosis inducing factor (AIF) and apoptotic cell death, 1212
- Apoptotic protease activating factor-1 (APAF-1) and apoptotic cell death, 1212
- AR. *See* Androgen receptor (AR)
- Argyrophilic nucleolar organizer regions (AgNORs), 1479
- Armed Forces Institute of Pathology (AFIP), 976
- ARMS. *See* Alveolar RMS (ARMS)
- Arteriovenous hemangioma (arteriovenous malformation)
 clinical findings, 776–777
 differential diagnosis, 778–779
 imaging, 777
 immunohistochemistry, 778
 pathologic findings, 777–778
 prognosis and treatment, 779
- Arthralgia, 253
- Aspergillosis
 acute fulminant invasive, 1630
 chronic invasive/chronic granulomatous, 1631–1632
 histopathology, 1630–1631
 historical background, 1629–1630
 serology, 1631
 treatment, 1631
- Aspergillus flavus*, 1630
- Aspergillus fumigatus*, 354
- Aspirin, 968
 intolerance, 346–347
- ASPS. *See* Alveolar soft part sarcoma (ASPS); Alveolar soft part sarcoma (ASPS)
- Asteroid bodies, 1693
- Ataxia-telangiectasia (AT), 1667
- Ataxia-telangiectasia syndrome, 1523
- AT-mutated (ATM) gene, 1667
- Atrophic rhinosinusitis (ARS), 346
- Atypia, 130
- Atypical carcinoid (AC), 164–166
 clinical features, 164
 diagnosis, 165
 electron microscopy, 165
 immunohistochemistry, 165
 pathology, 164
 treatment, 165–166
- Atypical fibroxanthoma (AFX), 463–464, 1494–1495
 clinical features, 1520
 differential diagnosis, 1521
 electron microscopy, 1521
 immunohistochemistry, 1521
 molecular genetics, 1521
 pathology, 1520–1521
 treatment and prognosis, 1521
- Atypical keratinocytes, 1489
- Atypical lymphoid hyperplasia, 1081
- Atypical lymphoreticular cells, 652
- Atypical marginal zone hyperplasia, of tonsil, 1093
- Atypical teratoid/rhabdoid tumor, 1363
- Auditory canal
 external. *See* External auditory canal
- malignant neoplasms of, 459–464
- Auricular cartilage
 of idiopathic cystic chondromalacia, 433–434
- Autoimmune diseases, 952
- Autoimmune hypoparathyroidism, 1460
- Autoimmune lymphoproliferative syndrome, 1024–1025
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), 1460

- Autoimmune polyglandular syndrome-1, 1460
- Autotransplantation, of parathyroid glands, 1462–1463
- Azathioprine, 257, 1693
- Azithromycin, 1689
- Bacillary Angiomatosis (BA)
clinical presentation, 1628
culture, PCR, and serological identification, 1628
differential diagnosis, 1628
etiology, 1628
histopathology, 1628
treatment, 1628
- Bacilli Calmette-Guerin (BCG), 1623
- Bacterial conjunctivitis, 72
- Bacterial meningitis, 654
- Bacterial sinusitis
acute, 1609
chronic, 1609–1610
- Band keratopathy, 1580
- Bartonella henselae*, 51, 1011
- Basal cell adenocarcinoma, 25, 564–567
- Basal cell adenoma, 23–24, 34
clinical features, 522–523
differential diagnosis, 525
electron microscopy, 524
immunohistochemistry, 524–525
overview, 522
pathology, 523–524
treatment, 525–526
- Basal cell carcinoma (BCC), 75–76, 459, 1342
clinical features, 1496
differential diagnosis, 1498
eyelids, 1552–1553
imaging studies, 1496
immunohistochemistry, 1497–1498
molecular genetics, 1498
pathology, 1496–1497
treatment and prognosis, 1498
- Basal cell nevus syndrome, 1342
- Basal cell type ameloblastoma, 1206–1207
- Basal encephaloceles*, 652
- Basaloid cells, 23
- Basaloid keratinocytes, 1475
- Basaloid squamous carcinomas, 309–312, 398. *See also* Squamous cell carcinomas
differential diagnosis, 311–312
histologic features, 309–310
immunohistochemistry, 311
treatment and prognosis, 310–311
- Basaloid squamous cell carcinoma, 62, 155–158
clinical features, 155
diagnosis, 157
electron microscopy, 157
etiology, 155
immunohistochemistry, 157
overviews, 155
pathology, 155–157
treatment, 157–158
- Basaloid tumors, 25
- Basement membrane-associated molecules
AOT and, 1238
and CEOT, 1234
- Basement membrane zone (BMZ), 246
- Basement-type heparan sulfate
proteoglycan (HSPG) and solid/
multicystic ameloblastoma–central,
1209
- Base of tongue, squamous cell carcinomas,
303–305
- Basidiobolus, 1638
- Basosquamous cell carcinoma (BSCC)
clinical features, 1498–1499
differential diagnosis, 1499
imaging studies, 1499
immunohistochemistry, 1499
pathology, 1499
treatment and prognosis, 1499
- B-cell lymphoma
intravascular large, 1042
primary mediastinal (thymic) large,
1041–1042
T-cell/histiocyte-rich large, 1042
- B-cells, 39
lymphoblastic leukemia/lymphoma, 1060
- Bcl-2 and inhibitor of apoptosis (IAP) family
proteins, modulators of
mitochondrial apoptotic pathway,
1212
- BCL2 protein expression, follicular
lymphoma, 1049
- Beckwith-Wiedemann syndrome, 1523
- Behcet's disease, 261
- Benign epithelial neoplasms
actinic keratoses (AKs), 1489–1491
cutaneous lymphadenoma (CL), 1482–1484
hidrocystomas, 1484–1485
pilar cysts (PCs), 1477–1478
pilomatricoma, 1479–1481
proliferating pilar cyst (PPC), 1478–1479
sebaceous adenoma, 1488–1489
sebaceous hyperplasia, 1487–1488
seborrheic keratoses (SKs), 1475–1477
syngoma, 1485–1487
trichilemmomas (TLs), 1481–1482
- Benign FHH, 1438
- Benign lymphoepithelial lesion (BLEL), 1661
- Benign lymphoepithelial tumor, of the skin.
See Cutaneous lymphadenoma (CL)
- Benign mesenchymal tumors
of external auditory canal, 448–449
- Benign mesenchymomas, 895
- Benign migratory glossitis, 205–207
clinical features, 206
diagnosis, 206
pathology, 206
treatment, 207
- Benign neoplasms, 1481
external auditory canal, 447–449
middle ear and temporal bone, 449–456
- Benign odontogenic tumors
adenomatoid odontogenic tumor,
1235–1240
ameloblastoma
desmoplastic ameloblastoma,
1218–1221
keratoameloblastoma, 1225–1226
papilliferous keratoameloblastoma,
1226–1228
solid/multicystic ameloblastoma–
central, 1202–1215
solid/multicystic ameloblastoma–
peripheral, 1215–1218
unicystic ameloblastoma, 1221–1225
calcifying epithelial odontogenic tumor,
1230–1235
squamous odontogenic tumor, 1228–1230
- Benign thyroid inclusions, in lymph node,
230–231
- Benzoylmethylecgonine. *See* Cocaine
- Ber-EP4 expression, 1499
- Bethanechol chloride, 1691
- Bilateral acoustic neuroma. *See*
Neurofibromatosis 2
- Biopsy
ABCD, 963
osteoblastoma, 970
PLCD, 963
- Biphasic synovial sarcoma. *See* Synovial
sarcoma
- Bipolaris, 1639–1640
- Birefringent oxalate crystals, 954
- Blastic plasmacytoid dendritic cell
neoplasm, 1077–1078
- Blastomycosis, 1642, 1648–1651
- Blue rubber bleb syndrome, 1523
- B- lymphocytes, 952, 953
- BMP. *See* Bone morphogenetic protein
(BMP), in ameloblastomas
- BMZ. *See* Basement membrane zone (BMZ)
- Bohn's nodules, 1343. *See also* Oral cavity
- Bone, hematolymphoid lesions of, 1108–
1109
- Bone morphogenetic protein (BMP), in
ameloblastomas, 1213
- Bone sialoprotein (BSP), in ameloblastomas,
1213
- Borrelia burgdorferi*, 953, 1692
- Botryoid rhabdomyosarcoma, 871
- Botulinum toxin, 1485
- Bowenoid papulosis, 1676
- Bowen's disease. *See* Squamous cell
carcinoma (SCC)
- BP-antigen, 249
- BRAF mutations, 1488, 1510
- Branchial cleft anomalies, 426–427
- Branchial cleft cyst, 21, 1351–1352
- Branchial complexes, 1429
- Branchiogenic carcinoma, 1155–1156
- BRD4-NUT fusion product, 1730
- BRD4 tumors, 1730
- BSP. *See* Bone sialoprotein (BSP), in
ameloblastomas
- Buccal mucosa
squamous cell carcinomas, 294–295
- Buccal nerve, 669
- Buccinator muscle, 669
- Bullous keratopathy, 1564–1565
- Bullous pemphigoid, 248–249
clinical presentation, 248
immunology, 249
immunopathology, 249
pathology, 248–249
treatment, 249
- Bulls eye, skin lesion, 258, 259
- Burkitt's lymphoma, 40–41, 1056–1057, 1355,
1667–1668
- Calcification, 1477, 1594
- Calcifying cystic odontogenic tumor
(CCOT)
adenomatoid odontogenic tumor–
associated, 1268
ameloblastic fibroma-associated, 1268
ameloblastic fibro-odontoma-associated,
1268
clinical features, 1269–1270
immunohistochemically studies, 1271
odonto-ameloblastoma-associated, 1269
odontogenesis stages of, 1270–1271
odontogenic fibromyxoma-associated,
1269
odontoma-associated, 1269
solid/multicystic ameloblastoma–
associated, 1267
treatment and prognosis, 1272
ultrastructure of, 1271
unicystic ameloblastoma-associated,
1267–1268
- Calcifying epithelial odontogenic tumor
(CEOT)
calcification and, 1233
clear-cell variant of, 1231–1233
differential diagnosis, 1235

- [Calcifying epithelial odontogenic tumor (CEOT)]
 etiology and source, 1232–1233
 extraosseous variant of, 1233
 immunohistochemistry
 CK antibody reaction, 1234
 epithelial membrane antigens (EMAs), 1234
 proliferation marker Ki-67, 1234
 tenascin, 1234
 molecular-genetic data, 1235
 prevalence and incidence, 1230
 radiographs of, 1231–1232
 radiolucent–radiopaque type, 1231
 treatment and prognosis, 1235
 ultrastructural studies, 1234–1235
- Calcifying odontogenic cyst (COC), 1262–1263
 etiology of, 1263
 immunohistochemical studies, 1264
 treatment and prognosis, 1267
- Calcimimetics, 1456
- Calcitonin-producing C cells, 1385
- Calcium channel blocking agents, 217–218
- Calcium pyrophosphate crystal deposition disease (CPCDD)
 pathologic features, 954
 radiologic features, 954
- Calcium pyrophosphate dihydrate (CPPD), gout, 443
- Calcium-sensing receptor (CaSR), 1435
- Calcium supplements, 1456
- Calretinin and ameloblastic epithelium, 1223
- Canalicular adenoma, 24
 clinical features, 531
 defined, 531
 differential diagnosis, 532
 immunohistochemistry, 532
 pathology, 531–532
 treatment, 532
- Cancer, 1438
 sarcoma staging, AJCC on, 863
- Candida albicans*, 289
- Candida albicans pseudohyphae*, 59
- Candidiasis, 1645–1646
- Canker sores. *See* Recurrent aphthous stomatitis (RAS)
- Capillary hemangioma in soft tissues of neck, 1358
- Capillary malformations, 1522
- Carboxyterminal fragments, 1436
- Carcinoembryonic antigen (CEA), 14, 1483
- Carcinoma ex pleomorphic adenoma, 583–586
- Carcinoma in situ (CIS), 130, 133–135, 269
 clinical features, 133
 introduction, 133
 molecular-genetic data, 134
 pathology, 133
 treatment, 134–135
- Carcinoma of unknown primary (CUP), 1147
 frequency, 1148
 metastase histology, 1150
- Carcinomas. *See also* Granulomas
 adenoid squamous, 313–314
 adenosquamous, 312–313
 exophytic papilloma and, 362–363
 inverted papilloma and, 366–368
 incidence, 367
 molecular biology in HPV-related, 290
 neuroendocrine, 322–323
 and OSP, 370–371
 papillary squamous, 316–318
 showing thymus-like
 differentiation, 1413
- [Carcinomas]
 spindle cell. *See* Spindle cell carcinomas (SPCC)
 squamous cell. *See* Squamous cell carcinomas
 staging in nasal vestibule, 373
 verrucous. *See* Verrucous carcinomas
- Carcinosarcoma, 586–588. *See also* Spindle cell carcinomas (SPCC)
- Cardiac myxomas, 1727
- Cardiovascular complications, associated with hyperparathyroidism, 1442
- Carney complex (CNC), 1726–1727
- Carotid body paraganglia (CBPG), 718–721
- Cartilaginous lesions, 974
- Caseating granulomas, 1012
- Caspase-8 apoptosis initiator, role in ameloblastomas, 1212
- CaSR gene, 1458
- Castleman disease
 hyaline-vascular, 1019–1021
 localized plasma cell, 1021–1022
 multicentric, 1009, 1022–1023
- Cataract, 72
- B-catenin stabilization, 1481
- Cat scratch disease (CSD), 51
 clinical features, 1627
 etiology, 1627
 histopathology, 1627–1628
 of lymph node, 1011–1012
 serology and PCR, 1628
 treatment, 1628
- Cavernous hemangiomas, 74, 1596–1597
- CBPG. *See* Carotid body paraganglia (CBPG)
- CCC. *See* Clear cell carcinoma
- C cells tumors
 hyperplasia, 1409–1410
 medullary thyroid carcinoma, 1410
 mixed medullary-follicular carcinoma, 1411
 mixed medullary-papillary carcinoma, 1411–1412
- CCLE. *See* Chronic cutaneous lupus erythematosus (CCLE)
- CCOC. *See* Clear cell odontogenic carcinoma (CCOC)
- CCOT. *See* Calcifying cystic odontogenic tumor (CCOT)
- CD31, 866, 867
- CD34, 866, 867
- CD3 and CD4-like moieties, 1435
- CD99 immunoreactivity, in ES/PNET, 737
- CD3 immunostains, 39
- CD20 immunostains, 39
- CD44s, inverted papilloma, 368
- CE. *See* Congenital epulis (CE)
- CEA. *See* Carcinoembryonic antigen (CEA)
- Cefixime, 1618
- Cell block, 39
- Cellular alterations, in dysplasia, 267
- Cellular hemangioma of infancy. *See* Infantile hemangioma (IH)
- Cellular neurothekeomas, 694, 695
- Cellular PA, 34–35
- Cellular schwannomas, 680
- CEMBLA. *See* Cementoblastoma (CEMBLA)
- Cementoblastoma (CEMBLA)
 differential diagnosis, 1290
 etiology of, 1289
 growth rate, 1288
 immunohistochemistry, 1290
 prevalence and incidence, 1288
 radiographic examination, 1288–1289
 treatment and prognosis, 1290
- Cemento-osseous dysplasia, 965–966
- Cemento-ossifying fibroma, 1279
- Central odontogenic fibroma (COF), 1276
 differential diagnosis, 1278–1279
 etiology of, 1277
 histochemical studies, 1278
 treatment and prognosis, 1280
 ultrastructure of, 1278
- CEOT. *See* Calcifying epithelial odontogenic tumor (CEOT)
- Cerebrospinal fluid (CSF), 672
 leak, 675
 rhinorrhea, 675
- Ceruminal gland adenocarcinomas, 462–463
- Ceruminal gland adenomas, 447
- Ceruminal gland neoplasms, 447–448
- Ceruminal gland pleomorphic adenomas, 447
- Ceruminal glands, 424
- Cervical adenopathy location, 1147–1148
- Cervical lymphadenitis, 1623
- Cervical lymph nodes, 144, 1147, 1148
 deep, 1135
 levels, 1135
 metastasis to, 299–300
 superficial, 1135
- Cervical thymoma
 clinical features, 1724
 imaging studies, 1724
 pathology, 1724
 treatment and prognosis, 1724–1725
- CFP-10 (culture filtrate protein 10), 1623
- CFS. *See* Chronic fatigue syndrome (CFS)
- CFTR. *See* Cystic fibrosis transmembrane conductance regulator (CFTR)
- CGH. *See* Comparative genomic hybridization (CGH)
- Chalazions, 73, 1553
- Charcot-Leyden crystals, 355
- Cheilitis glandularis, 490–491
- Chemical carcinogens, oral cancer, 286–288
 metabolism, 288
- Chemodectoma, 717
- Chemoreduction, 1594
- Chemotherapy, 983
- Chemotherapy-induced atypia, 1491
- Cherubism, 966–967
- Chlamydia, 72
- Chlamydial conjunctivitis, 72
- Chlorhexidine, 263
- Cholesteatomas
 acquired, 436–437
 congenital, 437–438
- Cholesterol granulomas, 30, 357–358
versus congenital cholesteatomas, 438
- Chondroblastomas, 69, 978–979
- Chondrocalcinosis. *See* Calcium pyrophosphate crystal deposition disease (CPCDD)
- Chondrodermatitis nodularis chronica helices (CNCH), 432–433
- Chondrodermatitis nodularis helices (CNH)
 clinical features, 1534
 differential diagnosis, 1535
 histologic features, 1534
 immunohistochemistry, 1534
 treatment and prognosis, 1535
- Chondroid metaplasia, 975–976
- Chondroma, 976
- Chondromatosis, synovial
 of temporomandibular joint, 435–436
- Chondromyxoid fibroma, 978
- Chondrosarcoma, 976–978
 larynx, 977
 law, 977
- Chordoid meningioma, 706
- Chordoma, 979–981
- Choroidal melanoma, 1589
- Choroid plexus, 675
- Choroquine, 1693

- Chromogranin, 67, 1452
 Chromosome 22q11 microdeletion syndrome, 1460
 Chronic bruxism, 958
 Chronic cutaneous lupus erythematosus (CCLE), 252
 Chronic diffuse sclerosing osteomyelitis, 960
 Chronic fatigue syndrome (CFS), 1666
 Chronic granulomatous fungal sinusitis, 1631
 Chronic hyperphosphatemia, in children, 963
 Chronic invasive fungal sinusitis, 1632
 Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 1059
 Chronic sclerosing osteomyelitis, 959–960
 Chronic sclerosing sialadenitis, 486–490
 of submandibular gland, 1097–1098
 Chronic sinusitis, 345
 Chronic suppurative osteomyelitis, 959
 Chronic suppurative otitis media (CSOM), 1612
 Churg-Strauss syndrome, 650, 657–660, 1610
 clinical features, 658
 criteria for diagnosis, 658
 limited form, 657
 pathology, 658–659
 treatment and prospect, 660
 Chvostek's sign, 1460
 Cidofovir, 1663
 Cigarette smoking, and salivary gland tumors, 506–507
 Ciprofloxacin, 1612
 Circumferential margin preparation, 98
 CIS. *See* Carcinoma in situ (CIS)
 Civatte bodies, 260
 CK. *See* Cytokeratin (CK)
 CK 5/6 expression, 1481
 CK 20-positive Merkel cells, 1483
 Cladosporium, 1640–1641
 Clark level of invasion, 1507
 Classical Hodgkin lymphoma, 45
 clinical features, 1032
 differential diagnosis, 1035
 immunohistochemistry, 1034–1035
 lymphocyte-rich, 1033–1034
 molecular genetic data, 1035
 oral cavity and oropharynx, 1089
 pathology, 1032–1034
 treatment and prognosis, 1035
 Classic butterfly rash, malar region, 252
 Clear cell carcinoma (CCC), 563–564, 1729
 Clear cell myoepithelial carcinoma (CMEC), 1729
 Clear cell odontogenic carcinoma (CCOC)
 differential diagnosis, 1304
 etiology and pathogenesis, 1302–1303
 gender ratio, 1302
 histochemical and immunohistochemical studies, 1303
 molecular-genetic data, 1304
 prevalence and incidence, 1301
 treatment and prognosis, 1304
 ultrastructural studies, 1303
 Clear cells
 change, 31–32
 lesions, 16–17
 meningiomas, 703
 of parathyroid glands, 1432
 Clindamycin plus surgical drainage, 1611
 Clinical staging system, for
 rhabdomyosarcoma, 876
 CLL/SLL. *See* Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Clofaimines, 1691
 Clofazimine, 1620, 1627
 CMN. *See* Congenital melanocytic nevi (CMN)
 CMV. *See* Cytomegalovirus (CMV)
 CNB. *See* Core needle biopsy (CNB)
 COC. *See* Calcifying odontogenic cyst (COC)
 Cocaine
 chronic intranasal inhalation, 663
 clinical features, 663–664
 crack cocaine, 663
 pathology, 664
 treatment and prospect, 664
 Coccidioidomycosis, 1646–1648
 COF. *See* Central odontogenic fibroma (COF)
 CO₂-laser evaporation, 275
 Collagen-1 α 1 gene, 1517, 1519
 Collagenous fibroma (desmoplastic fibroblastoma)
 clinical features, 843
 differential diagnosis, 845–846
 electron microscopic findings, 845
 immunohistochemistry, 844–845
 molecular findings, 845
 pathologic findings, 843–844
 prognosis and therapy, 846
 radiologic findings, 843
 Colloid cyst, of the thyroid glands, 1457
 Colloid nodule. *See* Nodular goiter
 Combined small cell neuroendocrine carcinoma, 167
 Common cold, 345
 Comparative genomic hybridization (CGH), 685
 malignant melanomas, 393
 studies of ITAC, 386
 Computed tomography (CT), 1
 Condyloma acuminatum, 212–214
 clinical features, 212
 diagnosis, 213
 electron microscopy, 213
 molecular genetic data, 213–214
 overviews, 212
 pathology, 213
 treatment, 214
 Condylomas, 1676
 Congenital abnormalities, ear, 425–427
 Congenital cholesteatomas, 437–438
 versus cholesterol granulomas, 438
 Congenital epibulbar melanocytic proliferations, 1560
 Congenital epulis. *See* Gingival GCT of newborn
 Congenital epulis (CE), 701
 Congenital granular cell tumor, 1345
 Congenital hemangioendothelioma.
 See Kaposiform hemangioendothelioma
 Congenital hemangiopericytoma, 1358
 Congenital hereditary lymphedema syndrome, 1523
 Congenital herniations, 674
 Congenital-infantile fibrosarcoma with spindle cell, 1361
 Congenital melanocarcinoma. *See* Melanocytic neuroectodermal tumor of infancy (MNTI)
 Congenital pleomorphic adenoma. *See* Salivary gland anlage tumor
 Congenital teratoid cyst, 1343
 Congo red stain, 14
Conidiobolus, 1638
Conidiobolus coronatus, 1638
Conidiobolus incongruus, 1638
- Conjunctiva
 anatomy, 1557
 diseases
 conjunctival intraepithelial neoplasia (CIN), 1558–1559
 limbal dermoid, 1562–1563
 melanoses and melanocytic proliferations, 1559–1562
 specimen handling, 1557–1558
 Conjunctival intraepithelial neoplasia (CIN), 1558–1559
 Contact granuloma, 111–112
 Contact ulcers, 111–112
 Conventional chordoma, 980
 Conventional osteosarcoma, 972
 Convexity meningioma, 703
 Cookie-bite appearance, of ASPS, 902
 Core needle biopsy (CNB), 39
 Cornea
 anatomy, 1563–1564
 biopsy of
 acanthamoeba keratitis, 1571–1572
 pterygium, 1573–1574
 stains for, 1571
 diseases
 bullous keratopathy, 1564–1565
 Fuchs dystrophy, 1566–1567
 graft failure, 1567–1569
 keratoconus, 1569–1570
 pseudophakia, 1565–1566
 stromal dystrophies, 1570–1571
 specimen handling, 1564
 Cortex, lymphoid follicles in, 997
 Cortical defects of mandible
 anterior buccal cortical defect (ABCD), 963
 anterior lingual cortical defect (ALCD), 963
 posterior buccal cortical defect (PBCD), 963
 posterior lingual cortical defect (PLCD), 962–963
 Corticosteroids
 as drug, 1390
 therapy, 1584, 1600, 1693, 1719
Corynebacterium diphtheriae, 346
 Cowden syndrome, 1348, 1481
 CPCDD. *See* Calcium pyrophosphate crystal deposition disease (CPCDD)
 Cranial fasciitis, 966, 1359
 Craniopharyngioma
 clinical features, 714
 diagnosis, 716
 overview, 714
 pathology, 715–716
 radiography, 714–715
 somatic genetics, 716
 treatment, 716–717
 Craniotomy, 957
 Cribiform, 24
 Cricoarytenoid joints, 953
 Cricothyroid joints, 953
 Crohn disease, 228–229
 Cryopreservation, of parathyroid tissue, 1462–1463
 Cryotherapy, 277
 Cryptococcosis, 1642, 1651–1652
Cryptococcus, 1013
 CSD. *See* Cat scratch disease (CSD)
 CSF. *See* Cerebrospinal fluid (CSF)
 CT. *See* Computed tomography (CT)
 CT scan
 acute suppurative osteomyelitis, 958
 chondroblastomas, 978
 chondromyxoid fibroma, 978
 chondrosarcoma, 977
 chordoma, 980
 chronic suppurative osteomyelitis, 959
 extragnathic osteosarcoma, 972

- [CT scan]
 hemangioma, 981
 ossifying fibroma, 970
 osteoblastoma, 969
 osteoid osteoma, 968
 parosteal osteosarcoma, 973
 PLCD, 963
 PVNS, 934
 relapsing polychondritis, 961
 rheumatoid arthritis, 952
 CUP. *See* Carcinoma of unknown primary (CUP)
 Curvularia, 1640
 Cutaneous angiofibroma. *See* Fibrous papules (FP)
 Cutaneous intravascular large B-cell lymphoma, 1111
 Cutaneous leiomyosarcoma, 877, 879
 Cutaneous lymphadenoma (CL)
 clinical features, 1482
 differential diagnosis, 1483–1484
 immunohistochemistry, 1483
 molecular genetics, 1483
 pathology, 1482–1483
 treatment and prognosis, 1484
 Cutaneous mastocytosis, 1112, 1113
 Cutaneous pseudolymphoma, 1112
 Cyclic adenosine monophosphate (cAMP), 688
 Cyclin-dependent kinase inhibitor 2A (CDKN2A), 1510
 Cyclophosphamide, 1693
 Cyclosporine, 217, 257
 therapeutic agents, 1344
 Cystadenocarcinoma, 568–572
 Cystadenoma, 538–540. *See also* Hidrocystomas
 Cystic fibrosis, 352–354
 clinical features, 353
 nasal polyps with, 353
 pathology, 353–354
 of salivary glands, 478–479
 treatment, 354
 Cystic fibrosis transmembrane conductance regulator (CFTR), 353
 Cystic hygroma-lymphangioma and cystic hygroma colli, 1357
 Cystic lesions, 15–16, 21–22
 Cystic nests, 1552
 Cystogenic type SCC, 1299
 histopathology of, 1300
 treatment and prognosis, 1301
 ultrastructure of, 1301
 Cysts, 115–119
 ductal, 116
 epithelial, 117
 oncocytic, 117
 saccular, 116
 tonsillar, 117
 Cytochrome *c* oxidase defects, 1433
 Cytokeratin 8, 18, and 19, 1434
 Cytokeratin (CK), 31, 983
 expression in sinonasal tumors, 379
 Cytologic atypia, 1475, 1476
 in ASPS, 902
 Cytomegalovirus (CMV), 495–497, 1661
 in AIDS, 1662
 congenital, 1661–1662
 epidemiology, 1661
 in the head and neck, 1662–1663
 histopathology, 1663
 infection, 1007–1008
 infection in organ transplant recipients, 1662
 pathogenesis, 1663
 serology, 1663
 treatment, 1663
 Cytomegalovirus lymphadenitis, 1007–1008
 Cytometry, 15
 Dalen-Fuchs nodules, 1584
 Dapsone, 251, 263, 1627
 Debridement, of infected tissues, 1637
 Dedifferentiated liposarcoma, 884
 Deep lymph nodes
 lateral, 1135
 medial, 1135
 Deep or subcutaneous granuloma annulare (DSGA), 1367
 Dendritic cell neoplasm
 blastic plasmacytoid, 1077–1078
 Dendritic cell sarcoma, 1075–1079
 in cervical lymph node, 1153
 follicular, 1075–1076
 interdigitating, 1076–1077
 rare types of, 1078–1079
 De novo malignancies, 958
 Dental factors, oral cancer, 288–289
 Dental lamina cyst, 1343
 Dentinogenic ghost cell tumor (DGCT), 1272
 β -catenin gene mutation, 1275
 etiology of, 1273–1274
 histomorphological pattern of, 1275
 immunohistochemistry, 1274–1275
 treatment and prognosis, 1275
 ultrastructure of, 1275
 Dentinoid, and COC, 1265
 Denture-induced fibrous hyperplasia. *See* Fibrous hyperplasia, denture-induced
 Depositional diseases, of joints. *See* Inflammatory diseases, of joints
 De Quervain's thyroiditis, 1392
 Dermatofibroma (DF), 1482
 clinical features, 1515
 differential diagnosis, 1517
 electron microscopy, 1517
 immunohistochemistry, 1516–1517
 molecular genetics, 1517
 pathology, 1515–1516
 treatment and prognosis, 1517
 Dermatofibrosarcoma protuberans (DFSP), 687, 697, 880
 clinical features, 1518
 defined, 1517
 differential diagnosis, 1519
 electron microscopy, 1519
 imaging studies, 1518
 immunohistochemistry, 1519
 molecular genetics, 1519
 pathology, 1518–1519
 treatment and prognosis, 1519–1520
 Dermatopathic lymphadenopathy, 1005
 Dermoid cysts, 73, 957, 1596
 in periorbital nodule in infant, 1342–1343
 DESAM. *See* Desmoplastic ameloblastoma (DESAM)
 Desmin, 903, 904
 Desmoglein 1 (DG1), 246
 Desmoglein 3 (DG3), 246
 Desmoid fibromatosis, 1360
 Desmoplastic ameloblastoma (DESAM)
 Akt-signaling pathway and MAPKs, role in, 1220
 differential diagnosis, 1221
 etiology of, 1219
 immunohistochemistry, 1219
 intraosseous cystic/solid and, 1220
 prevalence and incidence, 1218
 radiological study, 1218–1219
 treatment strategy for, 1221
 Wingless type 1 glycoprotein (Wnt1) and SDC-1, 1220–1221
 Desmoplastic fibroma, 987–988, 1279
 Desmoplastic trichoepithelioma, 1500
 Desquamative gingivitis, 249, 255
 DFSP. *See* Dermatofibrosarcoma protuberans (DFSP)
 DG1. *See* Desmoglein 1 (DG1)
 DG3. *See* Desmoglein 3 (DG3)
 DGCT. *See* Dentinogenic ghost cell tumor (DGCT)
 Diabetic microangiopathy, 1637
 Diff-Quik, 1445
 Diffuse infiltrative lymphocytosis syndrome (DILS), 1660
 Diffuse large B-cell lymphoma (DLBCL), 15, 41–42, 1039–1045. *See also* Large cell lymphoma with chronic inflammation, 1043
 clinical features, 1039
 differential diagnosis for, 1044–1045
 elderly population with EBV-positive, 1043–1044
 immunohistochemistry, 1041
 large B-cell lymphoma, 1041–1043
 molecular genetic data, 1041
 pathology, 1039–1041
 primary cutaneous, 1043
 primary effusion lymphoma, 1044
 of thyroid, 1102
 primary cutaneous, leg-type, 1110–1111
 of tonsil, 1094
 treatment and prognosis, 1045
 Diffuse neurofibroma (DNF), 686–687
 DiGeorge syndrome, 1387, 1460
 Dilantin. *See* Diphenylhydantoin
 antiepileptic drug
 Dilator pupillae smooth muscle fibers, 1586
 Diphenylhydantoin antiepileptic drug, 1386
 Discoid lupus erythematosus, 1491. *See also* Chronic cutaneous lupus erythematosus (CCLE)
 Distant metastases from SCC, 1158–1159
 DLBCL. *See* Diffuse large B-cell lymphoma (DLBCL)
 Dopamine agonist medications, for pituitary adenomas, 712
 Down syndrome, 1342, 1388, 1486
 Doxycycline, 1628
 DQ stain, 5
 Drug-induced gingival hyperplasia. *See* Gingival hyperplasia, drug-induced
 DSGA. *See* Deep or subcutaneous granuloma annulare (DSGA)
 Ductal cells, 20, 27
 Ductal cysts, 116
 Ductal eccrine carcinoma. *See* Microcystic adnexal carcinoma (MAC)
 Ductal papillomas
 intraductal, 535–537
 inverted ductal papilloma, 538
 sialadenoma papilliferum, 537–538
 Dyshormonogenetic goiters, 1391
 Dyskeratosis, 130
 Dysphagia, 243
 Dysplasia, 267
 cellular alterations, 267
 genetic changes in, 273
 malignant transformation, correlation with, 272–273
 mild, 269
 moderate, 269
 severe, 269
 with three grades, 269
 tissue alterations, 267
 WHO classification, 269–270
 Dystrophic calcifications, 715, 954–955, 1344

- EAF. *See* Eosinophilic angiocentric fibrosis (EAF)
- Ear, 953
 external, 423–424
 hematolymphoid lesions of, 1107–1108
 inner, 424–425
 middle, 424
 neoplastic lesions of, 446–467
 benign neoplasms, 447–456
 endolymphatic sac papillary tumor, 457–458
 malignant neoplasms, 459–467
 nonneoplastic lesions, 425–432
 acquired, 427–432
 congenital abnormalities, 425–427
 squamous cell carcinomas, 459–460
- EBA. *See* Epidermolysis bullosa acquisita (EBA)
- EBV. *See* Epstein-Barr virus (EBV)
- EBV nuclear antigens (EBNA), 1665
- EBV-positive DLBCL, of elderly, 1043–1044
- Eccrine hidrocystomas, 1484
- Eccrine poroma, 1476, 1482
- ECRS. *See* Eosinophilic chronic rhinosinusitis (ECRS)
- ECS. *See* Extracapsular spread
- Ectopic acinic cell carcinoma, 1152
- Ectopic benign thyroid tissue, in nonlymphoid tissues, 231–232
 clinical features, 231–232
 pathology, 232
 treatment, 232
- Ectopic hamartomatous thymoma–branchial anlage mixed tumor
 clinical features, 1725
 differential diagnosis, 1726
 immunohistochemistry, 1726
 pathology, 1725–1726
 treatment and prognosis, 1726
- Ectopic lacrimal glands, 74
- Ectopic protrusion, 676
- Ectopic thyroid, 229–232
 benign thyroid inclusions, in lymph node, 230–231
 benign thyroid tissue, in nonlymphoid tissues, 231–232
 lingual thyroid, 229–230
- Edema, 250
- EH. *See* Epithelioid hemangioendothelioma (EH)
- EKH-6, 1486
- Electron microscopy
 of ITAC, 386
 of SCNEC, 381
 of SNUC, 379
- ELISA. *See* Enzyme-linked immunosorbent assays (ELISA)
- EM. *See* Erythema multiforme (EM)
- EMA. *See* Epithelial membrane antigen (EMA)
- Embryology
 of external ear, 423
 of inner ear, 424
 of middle ear, 424
- Embryonal rhabdomyosarcoma, 1361–1362
- Embryonal RMS (ERMS), 869, 870–871
- EMC. *See* Epithelialmyoepithelial carcinoma (EMC)
- EMC-degrading serine proteinases role in ameloblastomas, 1214
- EMMPRIN. *See* Extracellular matrix metalloproteinase inducer (EMMPRIN)
- Enamelin and calcifying odontogenic cyst (COC), 1265
- Enamel proteins
 in AFOD, 1251
 and AOT, 1238
 CEOT, 1234
- Enamelysin and calcifying odontogenic cyst (COC), 1265
- Encephalocele, acquired, 440
- Encephaloceles, 674
 nasal. *See* Nasal encephalocele
- Endemic goiters, 1391
- Endodermal sinus tumor, 1365–1366
- Endodontic therapy, 959, 960
- Endolymphatic sac papillary tumor, 457–458
- Endoneurial fibroblasts, 677
- Endophytic growth, of the tumor, 1593
- Endoscopic sinus surgery, 1609
- Endothelial cells, 981, 983
- Enneking staging system, for musculoskeletal sarcoma, 863
- Entomophthorales
 clinical course, 1637
 epidemiology, 1637
 histopathology, 1637
 serology, 1637
 treatment, 1637
- Enucleation
 categorizations for, 1577
 indications, 1577
 phthisis bulbi
 clinical features, 1579
 pathology, 1579–1582
 specimen handling, 1577–1579
 sympathetic ophthalmia, 1583–1586
 traumatic injury, 1582–1583
- Enzyme activity, 669
- Enzyme-linked immunoabsorbant assay (ELISA), 246, 650
- Eosinophilic angiocentric fibrosis (EAF), 359–360
- Eosinophilic chronic rhinosinusitis (ECRS), 354–355
- Eosinophilic granulomas, 438–439, 989
- Eosinophilic ulcer, of tongue, 1093
- Eosinophils, 660
- Eosin stains, 1445
- Ependyma, 675
- Epibulbar conjunctival stroma, 1557
- Epidermal nevus, congenital and acquired lesions, 1341
- Epidermolysis bullosa acquisita (EBA), 243
- Epistaxis, 1157
- Epithelial atrophy, 253
- Epithelial cysts, 117
- Epithelial dysplasia, nasal polyps, 350
- Epithelial-lined cysts, 1342
- Epithelial membrane antigen (EMA), 42–43, 1483
- Epithelialmyoepithelial carcinoma (EMC), 31, 561–563
- Epithelial-myoeplithelial carcinoma (EMEC), 1729
- Epithelioid cell sarcomas. *See* Polygonal cell sarcomas
- Epithelioid hemangioendothelioma (EH), 61, 863–867, 981–982
- Epithelioid hemangioma, 61, 1357
 in dermis and soft tissues of temporal region, 1359
- Epithelioid histiocytes, 1584
- Epithelioid tumor cells, 864
- E-2 promotor-binding factor-1 (E2F-1) and phosphorylated RB role in ameloblastomas, 1211
- Epstein-Barr virus (EBV), 41, 155, 160, 660, 1150, 1483, 1661. *See also* Human papillomavirus (HPV)
 clonal infections, 1665
- [Epstein-Barr virus (EBV)]
 disease associated with, 1664
 EBV-lymphoproliferative disorders, 1667–1668
 infectious mononucleosis, 1666–1667
 inverted papilloma, 363
 latent infections, 1664–1665
 nasopharyngeal carcinoma, 1668–1669
 nasopharyngeal carcinomas, 398
 oral hairy leukoplakia, 1669–1670
 overview and pathobiology, 1663–1664
 proteins, 1665–1666
 severe chronic active EBV infection, 1667
 sinonasal NK/T-Cell lymphoma, 1670–1671
 strains of, 1664
 undifferentiated salivary lymphoepithelial carcinoma, 1669
- Epstein-Barr virus–encoded RNA (EBER), 398
- Epstein's pearls, 1343. *See also* Oral cavity
- ER. *See* Estrogen receptor (ER)
- ERMS. *See* Embryonal RMS (ERMS)
- Erosive lichen planus, 250
- Eruptive vellus hair cyst, 1343, 1363
- Erythema, 250
- Erythema multiforme (EM), 258–261
 clinical presentation, 258–259
 diagnosis, 260–261
 etiology, 260
 pathology, 260
 treatment, 261
- Erythromycin, 1628
- Erythroplakia, 131, 275–277
 clinical features, 276
 defined, 275
 diagnosis, 277
 pathology, 276–277
 treatment, 277
- ESAT-6 (early secretory antigenic target protein 6), 1623
- ES/PNET. *See* Ewing's sarcoma and primitive neuroectodermal tumor (ES/PNET)
- Estrogen receptor (ER), 31
- Eustachian tube, 424
- Evan's tumor. *See* Low-grade fibromyxoid sarcoma (LGFMS)
- Ewing sarcoma–primitive neuroectodermal tumor (EWS-PNET), 1347
- Ewing's sarcoma, 55, 989
- Ewing's sarcoma and primitive neuroectodermal tumor (ES/PNET)
 clinical features, 735
 diagnosis, 737–738
 histopathology, 736
 imaging, 735–736
 immunohistochemistry, 736–737
 macroscopy, 736
 overview, 735
 somatic genetics, 737
 treatment, 738
 ultrastructure, 736
- EWS-PNET. *See* Ewing sarcoma–primitive neuroectodermal tumor (EWS-PNET)
- Excision, 677
- Excisional biopsy, hematolymphoid neoplasms, 1031
- Exophytic growth, of tumor, 1593
- Exophytic papilloma, 362–363
 and carcinomas, 362–363
 HPV incidence in, 363
- Exostosis, 967
 external auditory canal, 434–435
- Explosive follicular hyperplasia, of lymph node, 1009
- Exserohilum, 1639–1640

- External auditory canal
benign mesenchymal tumors of, 448–449
benign neoplasms, 447–449
cholesteatomas of, 437
exostosis, 434–435
squamous cell carcinomas of, 460–462
squamous cell carcinomas staging in, 462
- External ear, 423–424
malignant neoplasms of, 459–464
- Extracapsular spread (ECS), 1137, 1138–1140
- Extracellular matrix metalloproteinase inducer (EMMPRIN), and ameloblastomas, 1214
- Extracellular matrix proteins
in AMFs, 1244
and AOT, 1238
- Extracranial teratomas, 674
- Extragnathic osteosarcoma, 972–973
- Extramedullary hematopoietic tumor, 1026–1027
- Extramedullary plasmacytoma, 1057–1059
clinical features, 1057
differential diagnosis, 1057–1059
ectopic pituitary adenoma, 1059
immunohistochemistry, 1057
molecular genetic data, 1057
pathology, 1057
treatment and prognosis, 1059
- Extranodal marginal zone B-cell lymphoma, 604–607, 1600–1601
- Extranodal metastases
head and neck skin, 1157
laryngeal, 1157–1158
metastatic tumors, to eyes, 1157
metastatic tumors, to nasal cavity, 1157
metastatic tumors, to oral regions
jaw metastases, 1156
oral soft tissue metastases, 1156–1157
metastatic tumors, to paranasal sinuses, 1157
salivary glands, 1156
temporal bones, 1157
- Extranodal NK/T-cell lymphoma
nasal, 1060–1064
clinical features, 1061
differential diagnosis, 1062–1063
immunohistochemistry, 1061
molecular genetic data, 1061–1062
pathology, 1061
treatment and prognosis, 1063–1064
of oral cavity and oropharynx, 1089
of skin, 1111, 1112
- Extranodal sites
head and neck, 1001
HIV-associated lymphoid hyperplasia in
head and neck, 1010–1012
reactive lymphoid hyperplasia of, 1001
- Extrasosseous odontomas, 1253
- Extrasosseous osteosarcoma, 974
- Extravascular proliferation, of atypical endothelial cells, 868
- Eye, hematolymphoid lesions of, 1103–1107
clinical features, 1104
diagnostic considerations, 1107
neoplasms, 1103–1105
reactive/inflammatory, 1105–1107
- Eyelids
anatomy, 1551
diseases
basal cell carcinoma, 1552–1553
reactive inflammatory processes, 1553–1554
sebaceous neoplasms, 1554–1556
sebaceous tumefactions, 1553
squamous cell carcinoma, 1553
xanthelasma, 1557
specimen handling, 1551–1552
- Fabry's syndrome, 1523
- Facial bones. *See* Jaw
- Factitial rhinosinusitis, 348
- Familial hypocalciuric hypercalcemia (FHH), 1436
clinical features, 1457
differential diagnosis, 1458
molecular biology, 1458
pathologic features, 1457
treatment and prognosis, 1458
- Familial isolated hyperparathyroidism (FIHP), 1437–1438
- Fat stains, 1446
- FD. *See* Fibrous dysplasia (FD)
- Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC), France, 862
- Fetal development and thyroid gland growth, 1429
- Fetal rhabdomyoma, 1361–1362
- FGF. *See* Fibroblast growth factors (FGF), in ameloblastoma
- FHH. *See* Familial hypocalciuric hypercalcemia (FHH)
- Fibrinogen, 257
- Fibroblast growth factors (FGF), in ameloblastoma, 1211
- Fibroblastic-myofibroblastic tumors, 1358
- Fibrodysplasia ossificans progressive (myositis ossificans progressive)
clinical findings, 820–821
differential diagnosis, 821
immunohistochemistry, 821
pathologic findings, 821
prognosis and treatment, 821–822
radiologic imaging, 821
- Fibromatosis colli (Torticollis), 1359
clinical features, 828
differential diagnosis, 830
electron microscopy, 830
imaging, 828
immunohistochemistry, 830
molecular findings, 830
pathology, 828
treatment and prognosis, 830
- Fibromatosis (desmoid)
clinical findings, 832
differential diagnosis, 833–834
imaging, 832
immunohistochemistry, 833
molecular findings, 833
pathologic findings, 832–833
prognosis and treatment, 834
- Fibro-osseous lesions, 68
- Fibrosarcoma, 885–892, 988–989
- Fibrosis, 1367
in osteoradionecrosis (ORN), 961
- Fibrous dysplasia (FD), 960, 964–965
- Fibrous hamartoma of infancy
clinical findings, 825
differential diagnosis, 826–828
electron microscopy, 826
imaging, 826
immunohistochemistry, 826
molecular findings, 826
pathologic findings, 826
prognosis and treatment, 828
- Fibrous hyperplasia, denture-induced, 218–220
clinical features, 219
pathology, 219
treatment, 220
- Fibrous papules (FP)
clinical features, 1513
defined, 1513
differential diagnosis, 1514
- [Fibrous papules (FP)]
electron microscopy, 1514
immunohistochemistry, 1514
pathology, 1513
treatment and prognosis, 1514
- Fibrous septa, 1487
- Fibrous stromal cells, 965
- Fibrovascular proliferation, 1579
- Fibroxanthoma, atypical, 463–464
- FIHH. *See* Familial hypocalciuric hypercalcemia (FHH)
- FIHP. *See* Familial isolated hyperparathyroidism (FIHP)
- Filaggrin, and COC, 1265
- Filobasidiella neoformans, 1651
- Fine needle aspiration biopsy (FNAB), 37, 1149
Hodgkin lymphoma, 45–46
- Fine-needle aspiration (FNA), 1, 101, 1599
cytology, hematolymphoid neoplasms, 1031
- FISH. *See* Fluorescence in situ hybridization (FISH)
- FISH studies, 40
- Flexner-Wintersteiner rosettes, 78
- Floor of the mouth, squamous cell carcinomas, 295–298
- Florid interfollicular immunoblastic proliferation, 1355
- Flow cytometry, in lymph nodes, 39–40
- Fluorescence in situ hybridization (FISH), 728
- Fluoroquinolone-resistant gonorrhea, 1618
- FLUS. *See* Follicular lesion of undetermined significance (FLUS)
- FN. *See* Follicular neoplasm (FN)
- FNA. *See* Fine needle aspiration (FNA)
- FNAB. *See* Fine needle aspiration biopsy (FNAB)
- FNA biopsy. *See* Fine-needle aspiration biopsy (FNAB)
- FNCLCC. *See* Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC), France
- Focal epithelial hyperplasia, 211–212. *See also* Heck's disease
- Focal lymphocytic thyroiditis, 1389
- Focal myositis
clinical features, 797
definition, 796
differential diagnosis, 798
immunohistochemistry, 797–798
laboratory studies, 797
pathology, 797
radiologic imagery, 798
treatment and prognosis, 798
- Focal osteoporotic bone marrow defect, 961–962
- Follicular carcinoma, 7
- Follicular cells, 3, 4
in thyroid gland, 1385
- Follicular dendritic cell sarcoma, 1075–1076
- Follicular hyperplasia, 1355
- Follicular lesion of undetermined significance (FLUS), 9
- Follicular lesions, 6–9
- Follicular lymphoma, 44–45
clinical features, 1045–1046
differential diagnosis, 1050
histologic grading and growth pattern, 1047–1049
immunohistochemistry, 1049
molecular genetic data, 1049
pathology, 1046
pediatric, 1050
primary cutaneous follicle center lymphoma, 1050
versus reactive follicular hyperplasia, 1051

- [Follicular lymphoma]
 in situ, 1051
 of tonsil, 1090
 transformation to high-grade lymphoma, 1049–1050
 treatment and prognosis, 1050
- Follicular neoplasm (FN), 7
 diagnosis, challenges, 7–8
- Follicular thyroid tumors
 follicular adenomas, 1402
 follicular carcinoma, 1402–1404
- Follicular variant of papillary carcinoma (FVPC), 7
- Folliculosebaceous cystic hamartoma, 1488
- Fomivirsen, 1663
- Fordyce granules, 201
- Foregut duplication cyst, 1348
- Foreign body granuloma, 73
- Formalin, 10
- Foscarnet, 1663
- Frontal encephaloceles*, 674
- Frontofacionasal dysplasia, 674
- Frozen-section diagnoses, 95–105
 accuracy, 96
 contraindications, 97
 errors, 96–97
 handling tissue sample, 95
 indications, 97
 intraoperative cytology, 97
 overviews, 95
 preparation technique, 95–96
 regional applications, 97–105
 lymph nodes, 100–101
 mucosal surfaces, 101
 parathyroid gland, 104–105
 peripheral nerves, 100
 salivary gland, 101–103
 surgical margins, 97–100
 thyroid gland, 103–104
- Frozen section interpretation, of
 parathyroid, 1444–1446
- Fuchs dystrophy, 1566–1567
- Fungal conjunctivitis, 72
- Fungal infection, 1013
- Fungus ball/mycetoma
 clinical presentation, 1632
 etiology, 1632
 histopathology, 1632
 PCR techniques, 1632–1633
 treatment, 1633
- Furstenberg test, 672
- Fusarium, 1641
- Fusobacterium necrophorum*, 1611
- FVPC. *See* Follicular variant of papillary carcinoma (FVPC)
- Ganciclovir, 1663
- Ganglion, 957
- GAP. *See* GTPase-activating protein (GAP)
- Gardner's syndrome, 967, 1480
- GCA. *See* Giant cell angiofibroma (GCA); Giant cell arteritis (GCA)
- GCDFP-15. *See* Gross cystic disease fluid protein-15 (GCDFP-15)
- GCOC. *See* Ghost cell odontogenic carcinoma (GCOC)
- GCOT. *See* Granular cell odontogenic tumor (GCOT)
- GCT. *See* Giant cell tumor (GCT); Granular cell tumor (GCT); Granular cell tumor (GCT)
- Genetic abnormality, in cystic fibrosis, 353
- Genetic linkage analyses, of hereditary PGL, 718
- Genetic mutations, in SH3BP2 gene, 966
- Germ cell neoplasms, 1364–1365
- Germinal centers, progressive transformation of, 1004–1005
- Ghost cell glaucoma, 72
- Ghost cell odontogenic carcinoma (GCOC), 1212, 1304. *See also* Ameloblastomas
 differential diagnosis, 1306
 etiology of, 1305
 immunohistochemistry, 1306
 molecular-genetic data, 1306
 prevalence and incidence, 1305
 radiographic picture, 1305
 treatment and prognosis, 1306
- Giant cells, 47
 fibroma, 222
 lesions, 69
- Giant cell angiofibroma (GCA), 1728
- Giant cell arteritis (GCA)
 angiography and ultrasonography, 1717–1718
 clinical features, 1717
 differential diagnosis, 1719
 laboratory tests, 1718
 pathology, 1718–1719
 treatment and prognosis, 1719
- Giant cell carcinoma (GCC), 161–162
- Giant cell granuloma, 984–985
- Giant cell-rich malignant fibrous histiocytoma, 889
- Giant cell-rich osteosarcomas, 984
- Giant cell tumor (GCT), 171–172, 984
- Gierke disease, 1392
- Gingiva, squamous cell carcinomas of, 298–300
- Gingival carcinoma, 300
- Gingival fibromatosis
 clinical features, 830–831
 differential diagnosis, 831–832
 electron microscopy, 831
 imaging, 831
 immunohistochemistry, 831
 molecular-genetic data, 831
 pathology, 831
 treatment and prognosis, 832
- Gingival GCT of newborn, 1344
- Gingival hyperplasia, drug-induced, 217–218
- Glasscock-Jackson classification, of glomus tumors, 452
- Glaucoma, 1574–1575
- Glaukomflecken, 1585
- Glial cells missing gene (GCMB), 1435, 1460
- Glial heterotopias, 672
- Gliosis of the inner retina, 1580
- Glomus jugulare. *See* Jugular paraganglioma
- Glomus tumors, 717
 clinical findings, 793
 differential diagnosis, 794–795
 electron microscopy, 793
 Glasscock-Jackson classification, 452
 immunohistochemistry, 794
 molecular findings, 794
 pathologic findings, 793
 prognosis and treatment, 795–796
 radiologic imaging, 793
- Glomus tympanicum. *See* Tympanic paraganglioma
- Glottic carcinoma, 139–142
- GLUT-1 expression, 1522
- GLY382Asp, 1487
- Glycosaminoglycans in ODOMYX, 1286
- Gnathic osteosarcoma, 971–972
- Goiterous thyroids, 1390
- Gonorrhea
 diagnosis of, 1618
 histopathology, 1618
- [Gonorrhea]
 transmission and epidemiology, 1617–1618
 treatment, 1618
- Gorham-Stout syndrome, 981
- Gorlin-Goltz syndrome, 1344
- Gout, 442–443
 pathologic features, 953–954
 radiologic features, 953
- Grading
 of follicular lymphoma, 1047–1049
 histologic, of sarcoma, 863
 of malignant mesenchymal tumors, 862–863
- Graft failure, 1567–1569
- Graft-versus-host disease (GVHD), 258
- Gram-negative bacteria, 64
- Granular cell ameloblastoma, 1206–1207
- Granular cell odontogenic tumor (GCOT), 1214, 1281
 clinical features, 1282
 differential diagnosis, 1283
 histopathology of, 1282
 immunohistochemical technique, 1282–1283
 surgical removal, 1283
 ultrastructure of, 1283
- Granular cell tumor (GCT), 54, 60–61, 698–701, 1344
 CE, 701
 malignant GCT, 700–701
- Granulomas. *See also* Carcinomas
 cholesterol, 30, 357–358
 eosinophilic, 438–439
 nasal polyps, 350
- Granulomatosis, 438–439
 Wegener's. *See* Wegener's granulomatosis
- Granulomatous inflammation, 1598
- Granulomatous lesions, 73
 chalazions, 73
 dermoid cyst, 73
 foreign body granuloma, 73
 sarcoidosis, 73
 Wegener's granulomatosis, 73
 Whipple's disease, 73
- Granulomatous lymphadenitis, 50
- Granulomatous thyroiditis, 1390, 1392
- Graves' disease, 5–6, 1388–1389, 1484
- Gross cystic disease fluid protein-15 (GCDFP-15), 31
- Gross-sampling errors, 96
- Gross total resection (GTR), 681
- Growth factors
 and AFOD, 1251
 in ODOMYX, 1286
- GTPase-activating protein (GAP), 688
- GTR. *See* Gross total resection (GTR)
- GVHD. *See* Graft-versus-host disease (GVHD)
- Haemophilus influenza*, 953
- Haemophilus influenzae*, 345
- Hairy polyp, 1348–1349
- Hairy tongue, 209–210
 clinical features, 209
 pathology, 210
 treatment, 210
- Hamartomas, 1348, 1536–1538
 respiratory epithelial adenomatoid, 360–361
- Hamazaki-Wesenberg inclusions, 1693
- Hansen's disease, 1625
- Haphazard tangles, of nerve fascicles, 677
- Hard palate, squamous cell carcinomas of, 300–301

- Hard tissue-related proteins
and AMFs, 1244
AOT, 1238
and CEOT, 1234
- Hashimoto's thyroiditis, 4, 1101–1102, 1102, 1103, 1387–1388
- Hassal's corpuscles, 1457
- Haversian canals, 960, 967
- H&E. *See* Hematoxylin and eosin (H&E)
- Heck's disease, 1675. *See also* Focal epithelial hyperplasia
- Heerfordt's syndrome, 1692
- Helicobacter pylori*, 261
- Hemangiomas, 126–127, 779–780, 981, 1355
in adults, 127
clinical features, 780–782
differential diagnosis, 786–788
imaging, 782
immunohistochemistry, 786
of infancy. *See* Infantile hemangioma (IH)
in infants, 126–127
pathology, 782–786
prognosis and treatment, 788
- Hemangiopericytoid vascular pattern
in mesenchymal chondrosarcoma, 896
in monophasic synovial sarcoma, 897
- Hemangiopericytomas, 74, 707
- Hemangiopericytoma/solitary fibrous tumor
clinical features, 848
differential diagnosis, 849–850
electron microscopy, 849
imaging, 848
immunohistochemistry, 848
molecular findings, 848–849
pathologic findings, 848
prognosis and treatment, 850
- Hematolymphoid neoplasms
of bone, 1108–1109
of ear, 1107–1108
of eye, 1103–1107
of head and neck
etiology, 1031
general features, 1029–1031
Hodgkin lymphomas, 1032–1039
myeloid/histiocytic/dendritic cell tumors, 1073–1079
non-Hodgkin lymphomas, 1039–1073
pathology, 1031
staging, 1031–1032
WHO classification, 1030
of hypopharynx, 1099–1100
of larynx, 1099
of lymph node, 1079–1081
diagnostic considerations, 1079–1081
nasal cavity and paranasal sinuses, 1081–1086
clinical features, 1081
diagnostic considerations, 1085–1086
reactive/inflammatory
hematolymphoid lesions, 1082–1085
nasopharynx, 1086–1088
diagnostic considerations, 1088
features of, 1086–1087
reactive/inflammatory
hematolymphoid lesions, 1087–1088
of ocular adnexa, 1103–1107
oral cavity and oropharynx, 1088–1094
diagnostic considerations, 1093–1094
features, 1088–1090
reactive/inflammatory
hematolymphoid lesions, 1091–1093
of salivary gland, 1094–1099
diagnostic considerations, 1098–1099
features of, 1094–1096
reactive/inflammatory
hematolymphoid lesions, 1096–1098
- [Hematolymphoid neoplasms]
of skin, 1109–1115
of thyroid, 1100–1103
of trachea, 1100
- Hematopoietic tumor, extramedullary, 1026–1027
- Hematoxylin, 1445
- Hematoxylin and eosin (H&E) stain, 95, 961
- Hemidesmosomal proteins, 251
- Hemophilus influenza*, 429, 1609
- Hemorrhagic detachment, of the choroid, 1586
- Heparanase, and ameloblastomas, 1214
- Hepatocyte growth factor (HGF) role in ameloblastomas, 1211
- Hereditary gingival overgrowth, 1344
- Her-2 expression, 1485
- Herpes simplex virus (HSV), 121, 260, 1008–1009, 1661
clinical course, 1671–1673
epidemiology, 1671
interference with cell-mediated immunity, 1672–1673
treatment, 1673
- Herpes simplex virus type I (HSV I), 262
- Herpetic whitlow, 1671–1672
- Heterophil test, 1666
- Heterotopia
of middle ear and mastoid, 427
of neuroglial tissue, 68
of salivary glands, 477–478
- HGF. *See* Hepatocyte growth factor (HGF)
- HHM. *See* Humoral hypercalcemia of malignancy (HHM)
- HHV-8 DNA, 1659–1660
- Hidrocystomas
clinical features, 1484
differential diagnosis, 1485
imaging, 1484
immunohistochemistry, 1485
pathology, 1484–1485
treatment and prognosis, 1485
- High-grade MEC, 28
- Highly active antiretroviral therapy (HAART), 1532, 1657
- Histiocytic necrotizing lymphadenitis, 1355.
See also Kikuchi lymphadenitis
- Histiocytic sarcoma, 1073–1074
- Histiocytosis, Langerhans cell, 438–439
- Histologic frozen-section slide, of surgical margin, 99
- Histologic grading, of sarcoma, 863
- Histoplasma capsulatum, 1652
- Histoplasmosis, 1652–1654, 1691
- HIV. *See* Human immunodeficiency virus (HIV)
- HIV-associated lymphadenopathy, 1009–1012
lymphocyte depletion in, 1009
- HIV-associated lymphoepithelial, of salivary glands, 1096
- HIV-associated lymphoid hyperplasia, in head and neck extranodal sites, 1010–1012
- HL. *See* Hodgkin's lymphoma (HL)
- HLA. *See* Human leukocyte antigens
- Hoarseness, as symptom of contact ulcers, 112
- Hodgkin lymphomas, 1032–1039, 1354
classical, 1032–1035
nodular lymphocyte-predominant, 1035–1039
versus PTGC, 1005
post transplant, 1073
Hodgkin's disease, 15
- Hodgkin's lymphoma (HL), 33, 38
- Hordeolum (stye), 1553
- Horn cysts, 1476
- HPV. *See* Human papilloma virus (HPV)
- HRPT2 mutations, 1453, 1457
- HSV. *See* Herpes simplex virus (HSV); Herpes simplex virus (HSV)
- HSV-1 exposure/infection, 1671
- HSV-2 exposure/infection, 1672
- HSV I. *See* Herpes simplex virus type I (HSV I)
- Human herpesvirus 6 (HHV6) lymphadenitis*, 1009
- Human immunodeficiency virus (HIV), 38, 1657–1658
clinical categories of, 1657
criteria for infection for adolescents and adults, 1657
epidemiology, 1655
primary infection and latency, 1656–1657
transmission, 1655
treatment, 1658
tropism, 1656
virion and genome, 1655–1656
- Human leukocytes antigens (HLA), 122, 649
- nasopharyngeal carcinomas, 395
- Human milk fat globulin-1 (HMFG1), 1485
- Human papilloma virus (HPV), 211, 273
in benign *vs.* dysplastic *vs.* malignant IP, 1681
detection rates
in laryngeal SCC, 1683
in oral cavity SCC, 1683
in oropharyngeal SCC, 1682
diseases, 1675–1684
genome, 1675
incidence
in exophytic papillomas, 363
in oncocytic schneiderian papillomas (OSP), 370
in inverted papillomas, 1679–1681, 1681
inverted papilloma, 364
life cycle, 1675
molecular biology carcinomas related to, 290
nasopharyngeal carcinomas, 398
nonkeratinizing carcinomas, 376
pathobiology, 1674–1675
subtypes 16 and 18, 1559
transmission, 1673–1674
- Humoral hypercalcemia of malignancy (HHM), 1459
- Hurthle cell. *See also* Oncocytic neoplasms lesions, 1441
tumors
adenoma, 1404
carcinomas, 1404–1406
- Hyaline cartilage metaplastic, in mesenchymal chondrosarcoma, 896
- Hyaline PA, 35–36
- Hyaline-vascular Castleman disease, 1019–1021
clinical features, 1019
differential diagnosis, 1021
pathology, 1019–1021
- Hyalinization, 703
- Hyalinizing trabecular tumor
clinical features, 1400
differential diagnosis, 1401–1402
immunohistochemistry, 1401
microscopic features, 1401
molecular genetics, 1401
pathology of, 1400–1401
treatment and prognosis, 1402
- Hyalohyphomycosis, 1641
- Hyams grading system, for ONB, 731
- Hybrid cysts, 1478
- Hybrid tumors, of salivary gland, 596–597
- Hydralazine, 252
- Hydroa vacciniforme-like lymphoma, 1072

- Hydrochloroquine, 1693
 Hydroxylsilylpyridinoline, urine concentrations, 959
 Hyoid bone, 16
 Hyperbaric oxygen therapy, 961
 Hypercalcemia, non-PTH causes of. *See* Non-PTH-related hypercalcemia
 Hyperfunctioning parathyroid glands multigland and multifocal disease, 1453–1455
 single-gland disease
 adenoma, 1446–1449
 atypical adenoma, 1449–1450
 carcinoma, 1450
 differential diagnosis and molecular pathology, 1450–1453
 Hyperkeratosis, 1677
 Hyperorthokeratosis, 253
 Hyperparakeratosis, 253
 Hyperparathyroidism, 985–986. *See also* Primary hyperparathyroidism; Secondary hyperparathyroidism
 Hyperparathyroidism-jaw tumor (HPT-JT) syndrome, 1437–1438
 Hyperplasia, 130
 adenoid, 225–226
 atypical, 271
 basal, 271
 fibrous. *See* Fibrous hyperplasia, denture-induced
 gingival. *See* Gingival hyperplasia, drug-induced
 papillary. *See* Inflammatory papillary hyperplasia
 parabasal cell, 271
 squamous, 271
 tonsillar, 222–225
 Hyperplastic dental follicles, 1279
 Hyperplastic nodules, 5, 7
 diagnosis, challenges, 7–8
 Hyperuricemia, 953
 Hypervascular follicular hyperplasia, 1009
 Hypointense meningiomas, 702
 Hypopharynx, hematolymphoid lesions of, 1099–1100
 Hypophysis. *See* Pituitary gland
- Iatrogenic KS, 1660
 ICR. *See* International classification of rhabdomyosarcoma (ICR)
 Idiopathic cervical fibrosis
 clinical features, 824
 differential diagnosis, 825
 electron microscopy, 825
 imaging, 824
 immunohistochemistry, 824
 pathology, 824
 treatment and prognosis, 825
 Idiopathic cystic chondromalacia, auricular cartilage, 433–434
 Idiopathic midline destructive disease (IMDD), 660
 Idiopathic orbital inflammation, 73, 1598
 IgE antibodies in allergic rhinosinusitis, 344–345
 IgG. *See* Immunoglobulin G (IgG)
 IgG4-related sclerosing disease, 1014–1015
 of nasopharynx, 1087–1088
 of ocular adnexa, 1105–1106
 of parotid gland, 1097–1098
 IHC. *See* Immunohistochemistry (IHC)
 IIF. *See* Indirect immunofluorescence
 IMDD. *See* Idiopathic midline destructive disease
 Immature teratoma, 1365
 Immotile cilia syndrome. *See* Primary ciliary dyskinesia (PCD)
 Immunoblastic lymphomas, 42
 Immunocytochemical stains, 14
 Immunocytochemical techniques, 1433
 Immunocytochemistry. *See* Cytometry
 Immunodeficiency-associated lymphoproliferative disorders, 1072–1073
 Immunoglobulin G (IgG), 245, 650
 Immunohistochemistry (IHC), 14
 ALK+ anaplastic large cell lymphoma, 1066–1067
 Burkitt lymphoma, 1056–1057
 classical Hodgkin lymphoma, 1034–1035
 of DLBCL, 1041
 extramedullary plasmacytoma, 1057
 extranodal NK/T-cell lymphoma, 1061
 follicular lymphoma, 1049
 of hyaline-vascular Castleman disease, 1021
 intestinal-type adenocarcinomas (ITAC), 386
 of Kikuchi lymphadenitis, 1016
 lymphoepithelial carcinomas (LEC), 382
 malignant melanomas, 393
 MALT lymphoma, 1055
 mantle cell lymphoma, 1053
 nasopharyngeal carcinomas, 398
 nodular lymphocyte-predominant Hodgkin lymphoma, 1037
 nonintestinal-type adenocarcinomas (non-ITAC), 388–389
 nonkeratinizing carcinomas, 377
 papillary adenocarcinomas of nasopharynx, 401
 of Rosai-Dorfman disease, 1024
 sinonasal undifferentiated carcinomas (SNUC), 378–379
 small cell neuroendocrine carcinomas (SCNEC), 381
 Immunostains, on synovial sarcoma, 898
 Immunosuppressive drugs, 251
 Immunosuppressive therapy, 249
 Incidental pituitary adenoma, 709
 Indirect immunofluorescence (IIF), 650
 Indolent T-lymphoblastic proliferation, of oral cavity and oropharynx, 1093
 Infantile fibrosarcomas, 885, 886
 Infantile hemangioma-hemangioendothelioma, 1355
 Infantile hemangioma (IH)
 clinical features, 1525
 defined, 1524
 differential diagnosis, 1526
 imaging studies, 1525
 immunohistochemistry, 1526
 molecular genetics, 1526
 pathology, 1525–1526
 treatment and prognosis, 1526
 Infantile myofibroma, 1355
 desmoid and diffuse type, 1360
 Infantile systemic hyalinosis, 1344
 Infectious arthritis, 953
 Infectious mononucleosis, 51, 1007, 1666–1667
 versus large cell lymphoma, 1088
 nasopharynx, 1087
 tonsil, 1091–1092
 Infectious rhinosinusitis, 345
 Infiltration, fatty, 20
 Infiltrative BCC, 1496
 Infiltrative fibroblastic disorders, 1344
 Inflammatory diseases, of joints, 952–957
 calcium pyrophosphate crystal deposition disease (CPCDD), 954
 dermoid cysts, 957
 [Inflammatory diseases, of joints]
 dystrophic calcification, 954–955
 ganglion, 957
 gout, 953–954
 infectious arthritis, 953
 oxalosis, 954
 pigmented villonodular synovitis, 956–957
 rheumatoid arthritis, 952–953
 synovial chondromatosis, 955–956
 synovial cysts, 957
 tumoral calcinosis, 954–955
 Inflammatory lesions
 chondrodermatitis nodularis helices, 1534–1535
 rhinophyma, 1532–1534
 rosacea, 1532–1534
 weathering nodule of the ear, 1535–1536
 Inflammatory malignant fibrous histiocytoma, 890
 Inflammatory myofibroblastic tumor, 172–173
 Inflammatory otic polyps, 431
 Inflammatory papillary hyperplasia, 220–221
 Inflammatory process, 661
 Inflammatory pseudotumor, of lymph node, 1025–1026
 Infliximab, 1693
 INF- α therapy, 1677
 Infundibular cyst, 1342
 Inner ear, 424–425
 Meniere disease, 445–446
 Insular carcinoma, 14
 Insulinlike growth factors (IGFs)
 expression and stroma of ameloblastomas, 1212
 Integrin
 and AOT, 1238
 solid/multicystic ameloblastoma-central, 1209
 Interdigitating dendritic cell sarcoma, 1076–1077
 Intergroup Rhabdomyosarcoma Study
 Postsurgical Clinical Grouping System, on RMS staging, 876
 Interleukin-1, 958
 International Classification Of Rhabdomyosarcoma (ICR), 54
 International Prognostic Index (IPI) Scoring System, 1031
 International Prognostic Index score, 1032, 1045, 1054, 1063
 Intestinal-type adenocarcinomas (ITAC), 383–387
 classification and survival, 384
 clinical features, 383–384
 differential diagnosis, 386–387
 electron microscopy, 386
 etiology, 383
 imaging, 384
 immunohistochemistry, 386
 molecular-genetic data, 386
 Paneth cells in, 386
 pathology, 384–386
 treatment and prognosis, 387
 variants of, 384–385
 Intracranial extension, 676
 Intracytoplasmic lumen formation, 1486
 Intraepithelial alterations, classifications, 267–272
 dysplasia classification, by WHO, 269–270
 Ljubljana classification, 271–272
 squamous intraepithelial neoplasia classification, 270
 Intraleisional mineralization, 1478
 Intralymphatic growth, in ASPS, 902

- Intraneural perineurioma, 697
 Intraocular conditions, 1576–1586
 Intraocular lymphoma, 1104–1105
 Intraoperative cytologic evaluations, 1445
 Intraoperative parathyroid hormone testing (IOPTH), 1455
 Intraosseous basal cell ameloblastoma, 1214
 Intraosseous tumors, of salivary gland, 597–598
 Intrathyroidal parathyroid glands, 1430
 Intravascular large B-cell lymphoma, cutaneous, 1111
 Intraventricular meningioma, 703
 Intubation granuloma, 111–112
 Inverted papilloma, 363–369
 carcinomas and, 366–368
 clinical features, 363–364
 differential diagnosis, 368
 etiology, 364
 imaging, 364
 Krouse staging system for, 369
 pathology, 364–366
 treatment and prognosis, 368–369
 Inverting papilloma, 1678
 Involucrin and calcifying odontogenic cyst (COC), 1265
 Involucrin expression, in TL, 1481
 Iodine therapy, 6
 Iridocyclotomy, 1587
 Iris root, 1587
 Iron pigment in thyroid follicular cells, 1393
 Irritation fibroma, 221–222
 Isoniazid, 252
 Isthmus-catagen cyst. *See* Pilar cysts (PCs)
 ITAC. *See* Intestinal-type adenocarcinoma (ITAC)
 Itraconazole, 1637
- Jaw, 68–70
 metastases, 1156
 Jeryl Lynn vaccine substrain, 1687
 JHF. *See* Juvenile hyaline fibromatosis (JHF)
 JNA. *See* Juvenile nasopharyngeal angiofibroma (JNA)
 JOC. *See* Juxtaoral organ of Chievitz (JOC)
 JOC vs Carcinoma, microscopic features, 671
 JTPG. *See* Jugulotympanic paragangliomas (JTPG)
 Jugular paraganglioma, 721
 Jugulotympanic paragangliomas, 451–454
 classification, 452
 Jugulotympanic paragangliomas (JTPG), 721–722
 Juvenile hemangioma. *See* Infantile hemangioma (IH)
 Juvenile hyaline fibromatosis (JHF), 1344
 Juvenile melanoma, 1340
 Juvenile nasopharyngeal angiofibroma (JNA), 1360–1361
 Juvenile onset laryngeal papillomatosis, 1677
 Juvenile xanthogranuloma, nasal cavity, 1085
 Juxtaoral organ of Chievitz (JOC)
 clinical features, 669
 diagnosis, 671
 embryology, 669
 histopathology, 670
 immunohistochemistry, 671
 macroscopy, 670
 overview, 669
 physiology, 669
 ultrastructure, 670–671
- Kaposiform hemangioendothelioma, 1357–1358
 clinical features, 1527
 defined, 1526–1527
 differential diagnosis, 1527
 electron microscopy, 1527
 imaging studies, 1527
 immunohistochemistry, 1527
 pathology, 1527
 treatment and prognosis, 1527–1528
 Kaposi-like infantile hemangioendothelioma. *See* Kaposiform hemangioendothelioma
 Kaposi sarcoma (KS), 63, 277, 1659–1660
 clinical features, 1530
 differential diagnosis, 1532
 electron microscopy, 1532
 imaging studies, 1530–1531
 immunohistochemistry, 1531–1532
 molecular genetics, 1532
 pathology, 1531
 treatment and prognosis, 1532
 in vascular transformation of sinuses, 1005–1006
 Karyotypes, 727
 Kassabach-Meritt syndrome, 1357, 1523
 Kawasaki disease, 1018–1019
 KCOT. *See* Keratocystic odontogenic tumors (KCOT)
 Keloids
 clinical features, 1512
 defined, 1511
 differential diagnosis, 1512–1513
 electron microscopy, 1512
 immunohistochemistry, 1512
 molecular genetics, 1512
 pathology, 1512
 treatment and prognosis, 1513
 Kenny-Caffey syndrome, 1460
 Keratin-filled clefts, 1678
 Keratinization, 715
 in MCE, 28
 Keratinized cells, 267
 Keratinized papilloma, 123–124
 Keratinizing squamous carcinoma, 100
 Keratinizing squamous cell carcinomas (KSCC), 285, 290
 pathologic features, 290–292
 variants of, 285
 Keratinocyte growth factor (KGF), congenital cholesteatomas, 438
 Keratinocytes, in seborrheic keratoses (SK), 1475
 Keratinocytic intraepithelial neoplasia (KIN). *See* Actinic keratoses (AKs)
 Keratinous cysts of infundibular type, 1342
 Keratoacanthoma, 1493–1494
 Keratoameloblastoma, 1225–1226
 Keratoconus, 1569–1570
 Keratocystic odontogenic tumors (KCOT), 1209, 1240
 Keratocystoma, 540–542
 Keratohyaline granules, 1486
 Keratoma. *See* Cholesteatomas, acquired
 Keratosis, 129–133
 atypia, 130
 CIS, 130
 clinical features, 131
 dyskeratosis, 130
 erythroplakia, 131
 histology, 129–130
 hyperplasia, 130
 KWD, 131
 KWOD, 131
 leukoplakia, 131
 overviews, 129
 parakeratosis, 130
 treatment, 132–133
- Keratosis obturans (KO), congenital cholesteatoma, 438
 Keratosis with dysplasia (KWD), 131
 Keratosis without dysplasia (KWOD), 131
 Keratotic plugging, 253
 Kikuchi-Fujimoto disease. *See* Histiocytic necrotizing lymphadenitis; Kikuchi lymphadenitis
 Kikuchi histiocytic necrotizing lymphadenitis, 1354
 Kikuchi lymphadenitis, 52, 1015–1016
 Ki-67 labeling in, 1452
 Killian polyps. *See* Antrochoanal polyps (ACP)
 Kimura disease, 1016–1018
 clinical features, 1016–1017
 differential diagnosis, 1017–118
 pathology, 1017
 of salivary glands, 1098
 KIT mutations, 1510
 Klebsiella ozaenae, 346
 Klebsiella pneumoniae, 64
 Klebsiella rhinoscleromatis, 1085
 Klippel-Trenaunay syndrome, 1523
 Koch's bacillus, 1621
 Koplick's spots, 1685
 Krouse staging system, inverted papilloma, 369
 KS. *See* Kaposi sarcoma (KS)
 Kursteiner's canals, 1431
 Kuttner tumor. *See* Chronic sclerosing sialadenitis
 Kviem test, 1693
 KWD. *See* Keratosis with dysplasia (KWD)
 KWOD. *See* Keratosis without dysplasia (KWOD)
- Lacrimal gland
 clinical findings, 1599–1600
 extranodal marginal zone B-cell lymphoma, 1600–1601
 lymphoproliferative processes, 1599
 Laminin and solid/multicystic ameloblastoma-central, 1208
 Langerhans cell histiocytosis (LCH), 438–439, 966, 1074–1075, 1351, 1415
 of bone, 1109
 dermatopathic lymphadenopathy, 1005
 Kimura disease, 1018
 of skin, 1112
 Langerhan's cells, 52, 438–439
 and CEOT, 1234
 sarcoma, 1075
 Langerhan's histiocytes, 52
 Large cell carcinoma, 591–593
 Large cell infiltrates, diffuse/nodular diagnosis, of hematolymphoid lesions of skin, 1113–1114
 Large cell lymphoma. *See also* Diffuse large B-cell lymphoma (DLBCL)
 anaplastic. *See* Anaplastic large cell lymphoma
 versus infectious mononucleosis, 1088
 problems in diagnosis of, 1093–1094
 Laryngeal candidiasis, 1645
 Laryngeal carcinoma, 144–145
 Laryngeal cartilages invasion, 144
 Laryngeal kaposi sarcoma (KS), 1660
 Laryngeal leiomyosarcoma, 876
 Laryngeal metastases, 1157–1158
 Laryngeal papilloma, 1677
 Laryngeal paragangliomas (LPG), 723–724
 Laryngeal TB, 1622
 Laryngoceles, 117–119
 Larynx, 953
 hematolymphoid lesions of, 1099

- Laser therapy, 277
- Latent membrane proteins (LMP), 1664, 1665
- Lateral aberrant thyroid tissue, 230
- Lateralization of cancer in nasal cavity, 372
- LCH. *See* Langerhans cell histiocytosis (LCH); Lobular capillary hemangioma (LCH)
- LE. *See* Lupus erythematosus (LE)
- LEC. *See* Lymphoepithelial carcinomas (LEC); Lymphoepithelial cysts (LEC)
- Leg-type, primary cutaneous DLBCL, 1110–1111
- Leiomyomas, 128–129, 1416
clinical findings, 802–803
differential diagnosis, 805–806
electron microscopy, 805
imaging, 803
immunohistochemistry, 804
molecular findings, 804–805
pathologic findings, 803–804
prognosis and treatment, 806
- Leiomyosarcomas, 58, 876–881
- Leishmania*, 1013, 1653, 1654
- Leishmaniasis, 1013
- Lemiere's disease, 1611
- Lens
anatomy, 1575
cataract, 1575–1576
- Lentigo maligna, 1507
melanoma, 1507–1509
- Lepromatous lymphadenitis, 1012
- Leprosy
clinical features, 1625
culture and PCR identification, 1627
differential diagnosis, 1627
head and neck manifestations, 1626
histopathology, 1626–1627
immunological considerations, 1625
Ridley Joplin criteria classification, 1625
treatment, 1627
- LESA. *See* Lymphoepithelial sialadenitis (LESA)
- Leser-Trelat, 1477
- Lesions
containing squamous cells, 27–28
in ocular adnexa, 72–74
- Leukoplakia, 59–60, 131, 273–275
clinical features, 273
defined, 273
diagnosis, 274
pathology, 274
treatment, 274–275
- Levamisole, 263
- LGFMS. *See* Low-grade fibromyxoid sarcoma (LGFMS)
- Lichenoid drugs, 255–256
- Lichen planus, 254–257, 281
clinical presentation, 254–255
immunology, 257
immunopathology, 257
lichenoid drugs, 255–256
pathology, 256–257
treatment, 257
- Limbal dermoid, 1562–1563
- Limited form of Wegener's granulomatosis (LWG), 654. *See also* Wegener's granulomatosis
- Lingual thyroid, 229–230
clinical features, 230
pathology, 230
primordium of thyroid, 1346
treatment, 230
- Lip cancer, 292–294
- Lipoadenomas, 1449
- Lipoblastoma, 1364
- Lipoid proteinosis, 1344
- Lipoma, 128
- Lipoma, lipoma variants, and reactive lipomatous lesions
clinical and pathology, 806–812
differential diagnosis, 812
immunohistochemistry, 812
molecular findings, 812
prognosis and treatment, 812
radiologic imaging, 812
- Lipomatosis, 482
- Liposarcomas, 881–885
- Lithium, 1438
and hypercalcemia/
hyperparathyroidism, 1458–1459
- Ljubljana classification, 269, 271–272
basal hyperplasia, 271
malignant lesions, 271
parabasal cell hyperplasia, 271
squamous hyperplasia, 271
- LMP. *See* Latent membrane proteins (LMP)
- LMP-1, nasopharyngeal carcinomas, 400
- Lobectomy, 13, 15
- Lobular capillary hemangioma, 227–228
clinical features, 227–228
diagnosis, 228
pathology, 228
treatment, 228
- Lobular capillary hemangioma (LCH), 1340
- Localized plasma cell Castleman disease, 1021–1022
- LOH. *See* Loss of heterozygosity (LOH)
- Loss of heterozygosity (LOH), 685
- Low-grade fibromyxoid sarcoma (LGFMS), 886, 888
- Low grade malignancies *vs.* PA, 36–37
- Low-grade MEC, 26
- LPG. *See* Laryngeal paragangliomas (LPG)
- LPL. *See* Lymphoplasmacytic lymphoma (LPL)
- Lupus erythematosus (LE), 252–254, 274
chronic cutaneous lupus erythematosus, 252
diagnosis, 253–254
histopathology, 253
subacute cutaneous lupus erythematosus, 252–253
systemic lupus erythematosus, 252
treatment, 254
- Lupus lymphadenitis, 1014
- Lupus vulgaris (LV), 1622
- LWG. *See* Limited form of Wegener's granulomatosis
- Lymphadenomas
lymphadenoma, 534–535
sebaceous lymphadenoma, 533–534
- Lymphadenopathies, 37, 49–52, 1627
cat-scratch disease, 51
dermatopathic, 1005
granulomatous lymphadenitis, 50
HIV-associated, 1009–1012
infectious mononucleosis, 51
Kikuchi lymphadenitis, 52
reactive lymphoid hyperplasia, 49–50
Rosai-Dorfman disease, 51–52
suppurative lymphadenitis, 50
toxoplasmosis, 50–51
- Lymphangioma, 788, 983–984
clinical and molecular features, 789
differential diagnosis, 792
electron microscopy, 792
imaging, 789–790
immunohistochemistry, 792
pathology, 790–792
prognosis and treatment, 792–793
- Lymphatic malformations (LM), 1522, 1597–1598
- Lymph nodes, 37–52, 100–101
ancillary studies, 39–40
B-Cell, non-Hodgkin lymphoma, 43–45
biopsy, 1150
causes of enlargement of head and neck, 998
clinical symptoms, 38
diagnosis, 38–39
FNA, non-Hodgkin lymphomas, 39
FNAB, Hodgkin lymphoma, 45–46
FNAB, non-Hodgkin lymphomas, 40–43
hematolymphoid neoplasms, 1079–1081
infarction, 1006
inflammatory pseudotumor, 1025–1026
lymphadenopathies, 49–52
metastatic neoplasms to cervical lymph nodes, FNAB, 46–49
nonspecific reactive lymphoid hyperplasia, 997–1003
normal, 997
patterns and etiology of reactive, 1080
reactive lymphoid hyperplasia of, 997
- Lymphoblastic leukemias/
lymphomas, 1060
- Lymphoblastic lymphoma, 40
- Lymphocyte depletion
classical Hodgkin lymphoma, 1034
in fine fibrosis, 1009
- Lymphocyte-rich classical Hodgkin lymphoma, 1033–1034
- Lymphocytic/histiocytic (L&H) cells, 1005
nodular lymphocyte-predominant Hodgkin lymphoma, 1037
- Lymphocytic thyroiditis, 3
- Lymphoepithelial carcinomas (LEC), 33, 160–161, 382–383, 593–595
- Lymphoepithelial cysts (LEC), 22, 481–482
- Lymphoepithelial lesions, 33
- Lymphoepithelial sialadenitis (LESA), 501–505
of salivary glands, 1096
- Lymphoepithelial sialadenitis *versus* MALT lymphoma, 1100
- Lymphoepithelial tumor. *See* Cutaneous lymphadenoma (CL)
- Lymphoepithelioma, in children, 1355
- Lymphoepithelioma-like carcinoma (LE-LC), 1483
- Lymphoid cells, 3, 32
- Lymphoid hyperplasia, 33
- Lymphoid proliferations, 1079–1081
atypical lymphoid hyperplasia in, 1081
- Lymphoid tissues, of Waldeyer ring, 1001
- Lymphoma, 15
- Lymphoplasmacytic lymphoma (LPL), 43, 1059–1060
- Lymphoproliferative disorders, immunodeficiency-associated, 1072–1073
- Lymphoproliferative processes, 1599
- Macroadenoma, 709
- Maffucci syndrome, 1523
- Magnet resonance imaging (MRI), 1
- MAI. *See* Mycobacterium avium-intracellulare (MAI); *Mycobacterium avium-intracellulare* (MAI)
- Mainstay therapy, 976, 983
- Major aphthae, 261
- Malakoplakia, 431–432
clinical course, 1690
etiology, 1690
histopathology, 1690–1691
treatment, 1691
- Malignant ectomesenchymoma, 1363

- Malignant epithelial neoplasms
 basal cell carcinoma, 1495–1498
 basosquamous cell carcinoma, 1498–1499
 merkel cell carcinoma (MCC), 1502–1504
 microcystic adnexal carcinoma, 1499–1501
 squamous cell carcinoma, 1491–495
 trichilemmal carcinoma (TLC), 1501–1502
- Malignant extrarenal rhabdoid tumor, 900–901
- Malignant fibrous histiocytoma (MFH), 57, 885–892
- Malignant GCT, 700–701
- Malignant lesions, in nasal cavity sinuses, 64–68
- Malignant lymphomas, 32–33, 38
- Malignant melanomas, 47–48, 80–81, 170–171, 391–394, 1587
 amelanotic, 392
 in children, 1341
 clinical features, 391–392
 differential diagnosis, 393
 etiology, 391
 immunohistochemistry, 393
 molecular-genetic data, 393
 oral, 323–326
 pathology, 392–393
 treatment and prognosis, 393–394
- Malignant mesenchymal tumors
 ASPS, 901–904
 fibrosarcoma, 885–892
 grading, 862–863
 malignant extrarenal rhabdoid tumor, 900–901
 malignant fibrous histiocytoma, 885–892
 malignant lipomatous, liposarcomas, 881–885
 malignant mesenchymoma, 894–895
 malignant skeletal muscle
 leiomyosarcomas, 876–881
 RMS, 869–876
 malignant triton tumor, 892–894
 malignant vascular
 angiosarcoma, 867–869
 epithelioid hemangioendothelioma, 863–867
 mesenchymal chondrosarcoma, 895–897
 staging, 863
 synovial sarcoma, 897–899
- Malignant mesenchymoma, 894–895
- Malignant neoplasms, 9–15
 anaplastic carcinoma, 14–15
 of external ear and auditory canal, 459–464
 insular carcinoma, 14
 lymphoma, 15
 medullary carcinoma, 13–14
 of middle ear, 465–467
 papillary thyroid carcinoma, 9–11
- Malignant odontogenic tumors
 ameloblastic carcinoma (AMCA), 1292
 differential diagnosis, 1295
 DNA microarray study, 1295
 etiology of, 1293–1294
 frequency of, 1293
 gender ratio, 1293
 growth rate, 1293
 immunohistochemistry, 1294
 locations of, 1293
 ultrastructure of, 1294
- metastasizing ameloblastoma (METAM), 1290
 age range, 1291
 growth rate, 1291
 histopathological features of, 1291
 immunohistochemistry, 1291–1292
 location of, 1291
 treatment and prognosis, 1292
 secondary (Dedifferentiated) AMCA, 1295
- Malignant oral lesions, 61–63
 basaloid squamous cell carcinoma, 62
 metastatic squamous cell carcinoma, 62–63
 nonepithelial tumors, 63
 PLGA, 63
 salivary gland lesions, 63
 squamous cell carcinoma, 61–62
- Malignant peripheral nerve sheath tumor (MPNST), 58, 688. *See also* Malignant triton tumor
 clinical features, 726
 diagnosis, 728
 histopathology, 727
 imaging, 726–727
 immunohistochemistry, 727
 macroscopy, 727
 overview, 725–726
 somatic genetics, 727–728
 treatment, 728
 ultrastructure, 727
- Malignant rhabdoid tumor (MRT), 1363
 in floor of mouth, 1364
- Malignant round cell neoplasms, 1363
- Malignant syringoma. *See* Microcystic adnexal carcinoma (MAC)
- Malignant triton tumor, 726, 892–894
- Malignant tumors, in ocular adnexa, 75–79
 ACC, 76
 basal cell carcinomas, 75–76
 Merkel cell tumor, 77
 metastatic carcinoma, 78–79
 orbital teratomas, 77
 retinoblastoma, 77–78
 sebaceous carcinoma, 76–77
 squamous cell carcinoma, 76
- MALT. *See* Extranodal marginal zone B-cell lymphoma (MALT)
- MALT lymphoma, 33
- Manchester clinical diagnostic criteria, for NF2, 690
- Mandible, cortical defects. *See* Cortical defects of mandible
- Mandibular margin, 99
- Mantle cell lymphoma
 clinical features, 1051–1052
 differential diagnosis, 1053–1054
 immunohistochemistry, 1053
 molecular genetic data, 1053
 pathology, 1052–1053
 treatment and prognosis, 105
- Mantle cell lymphoma (MCL), 40, 44
- Marginal zone lymphoma (MZL), 43
- Massachusetts General Hospital, 982
- Masson trichrome histochemical stain, 878
- Masson vegetant hemangioma. *See* Papillary endothelial hyperplasia
- Mastocytosis, cutaneous, 1112, 1113
- Mastoid, heterotopias of, 427
- Matrix metalloproteinase (MMP), 685
- Matrix metalloproteinases (MMP), and ameloblastomas, 1213–1214
- Matrix-rich microcirculation architecture, 1587
- Maxillary sinuses, squamous cell carcinomas of, 374–376
- Mayo Clinic, 96
- Mazabraud myxomas, 1728
- Mazabraud syndrome, 964, 1727–1728
- McCoy cell culture, 72
- McCune Albright syndrome, 964
- MCL. *See* Mantle cell lymphoma (MCL)
- Measles (rubeola), 1685–1687
- Mebendazole, 1690
- MEC. *See* Mucoepidermoid carcinomas (MEC)
- Medial pterygoid muscle, 669
- Median rhomboid glossitis, 207–208
 clinical features, 207
 diagnosis, 208
 pathology, 207–208
 treatment, 208
- Medium-sized cell infiltrates
 diagnosis, of hematolymphoid lesions of skin, 1114
- Medullary carcinoma, 13–14
- Medullary thyroid carcinoma (MTC), 1355, 1356, 1391, 1441, 1451
- Medullary thyroid carcinoma (MTC), 685
- Meibomian gland, 73
- Meige disease, 1523
- Melanin, 48
- Melanocytic lesions, in ocular adnexa, 79–81
 malignant melanoma, 80–81
 melanocytoma, 79–80
 melanotic neuroectodermal tumor of infancy, 79
- Melanocytic neoplasms
 melanomas, 1507–1511
 spitz nevus, 1504–1507
- Melanocytic neuroectodermal tumor of infancy (MNTI)
 clinical features, 733
 diagnosis, 734
 histopathology, 733–734
 imaging, 733
 immunohistochemistry, 734
 macroscopy, 733
 overview, 733
 somatic genetics, 734
 treatment, 734–735
 ultrastructure, 734
- Melanocytic nevi, cutaneous tumefactions from children
 atypical pattern of lentiginous proliferation, 1341
 congenital melanocytic nevi (CMN), 1339
 giant CMN, 1341
 nested and lentiginous junctional component, 1340
 neurocytic hamartoma, 1340–1341
 risk of a malignancy in, 1340
 single cell pattern, 1340
 spitz-like features, 1340
- Melanocytoma, 79–80
- Melanomas
 clinical features, 1507–1508
 differential diagnosis, 1511
 electron microscopy, 1510
 imaging studies, 1508
 immunohistochemistry, 1510
 molecular genetics, 1510
 pathology, 1508–1510
 staging, 1507
 treatment and prognosis, 1511
- Melanoses and melanocytic proliferations, 1559–1562
- Melanosis, 170
- Melanotic ameloblastoma. *See* Melanocytic neuroectodermal tumor of infancy (MNTI)
- Melanotic lesions, 170–171
- Melanotic neuroectodermal tumor of infancy, 1346
- Melanotic neuroectodermal tumor of infancy, 79
- Melanotic neuroectodermal tumor of infancy (MNTI), 1346
 vimentin and HMB45, 1347
- Melanotic progenoma. *See* Melanocytic neuroectodermal tumor of infancy (MNTI)
- Mel-CAM glycoprotein and calcifying odontogenic cyst (COC), 1265

- Membrane type 1-matrix metalloproteinase (MT1-MMP), and ameloblastomas, 1214
- Membranous labyrinth, 424–425
- Memorial Sloan-Kettering Cancer Center, 295, 305
- MEN. *See* Multiple endocrine neoplasia (MEN); Multiple endocrine neoplasia (MEN)
- Meniere disease, inner ear, 445–446
- Meningeal sarcoma, 706
- Meningioma
clinical features, 701–702
diagnosis, 707
imaging, 702
immunohistochemistry, 705
malignant, 704–705
overview, 701
pathology, 702–704
somatic genetics, 705–707
treatment, 707–708
WHO classification, 701
- Meningioma of the ocular adnexa, 1602
- Meningiomas, 75, 455–456
- Meningitis, bacterial, 676
- Meningoceles, 674
- Meningothelial cells, 704
- Merkel cell carcinoma (MCC)
clinical features, 1502
differential diagnosis, 1503–1504
electron microscopy, 1503
immunohistochemistry, 1503
molecular genetics, 1503
pathology, 1503
treatment and prognosis, 1504
- Merkel cell tumor, 77
- Mesenchymal chondrosarcoma, 895–897
- Mesenchymal tumors
angiosarcoma, 1415–1416
atypical fibroxanthoma, 1520–1521
dermatofibroma, 1515–1517
dermatofibrosarcoma protuberans, 1517–1520
fibrous papules (FPs), 1513–1514
keloids, 1511–1513
leiomyomas, 1416
nuchal-type fibroma, 1514–1515
- Mesenchymal tumors, benign
of external auditory canal, 448–449
- Metastases, 179
cervical lymph nodes, 299–300
clinical features, 179
nasal cavity/paranasal sinuses, 402
overviews, 179
prognosis, 179
- Metastases , of orbit, 1603
- Metastasizing ameloblastoma (METAM), 1290
- Metastatic adenocarcinoma, 1150
- Metastatic carcinoma, 25, 78–79, 1138
- Metastatic cystic squamous carcinoma, 1151, 1152
- Metastatic malignancies, 17–18, 31
- Metastatic melanoma, 1591
- Metastatic neoplasms to cervical lymph nodes, FNAB, 46–49
malignant melanoma, 47–48
nasopharyngeal carcinoma, 47
squamous cell carcinoma, 46–47
supraclavicular lymph node metastases, 48–49
thyroid carcinoma, 47
- Metastatic neuroblastoma, to skull, 1363
- Metastatic papillary carcinoma, of thyroid, 1151
- Metastatic squamous cell carcinoma, 62–63
- Metastatic thymoma, 1725
- Metastatic tumors, to oral regions
jaw metastases, 1156
oral soft tissue metastases, 1156–1157
- Metastatic tumors to middle ear and temporal bone, 467
- Metastatic tumors to thyroid, 1416–1417
- Metastatic undifferentiated nasopharyngeal type, of carcinoma, 1151
- Methimazole antithyroid drugs, 1386
- Methotrexate, 1693
- Methylene diphosphonate bone scintigraphy, 961
- Metronidazole, 1611
- MFH. *See* Malignant fibrous histiocytoma (MFH)
- MIB-1 antibody in AFOD, 1251
- Microcystic adnexal carcinoma (MAC), 1486–1487
clinical features, 1499
differential diagnosis, 1500
immunohistochemistry, 1500
molecular genetics, 1500
pathology, 1499–1500
treatment and diagnosis, 1500–1501
- Microinvasive carcinoma (MIC), 135–136
clinical features, 136
overviews, 135–136
treatment, 136
- Microscopy with laser excision, 1677
- Micronodular BCC, 1496
- Microscopic polyangiitis (MPA)
clinical features, 655
diagnosis, 655
pathology, 655
treatment and prospect, 655–656
- Middle ear, 424
adenocarcinomas, 466–467
adenomas. *See* Middle ear adenomas
benign neoplasms of, 449–456
cholesteatomas of, 436–438
endolymphatic sac papillary tumor, 457–458
heterotopias of, 427
malignant neoplasms of, 465–467
metastatic tumors, 467
squamous cell carcinomas, 465–466
- Middle ear adenomas, 449–451
with neuroendocrine differentiation, 450–451
- Middle ear squamous cell carcinomas, 465–466
- Midfacial destructive diseases, diagnosis of, 664
- Midline carcinoma with NUT rearrangement (MCNUTR), 1729–1730
- Mild dysplasia, 269
- Milial cysts, 1342
- Milk alkali syndrome, 1438
- Minimally invasive techniques, 1455
- Minocycline, 1693
- Minocycline ingestion and pigment accumulation in thyroid, 1393
- Minor aphthae, 261
- Minor aphthous ulcers, 261
- Mitomycin-C, 1556
- Mitoses, 1480, 1726
- Mitotic activity, 1493
- Mixed mesoneuroectodermal hamartoma, 1348
- MMP. *See* Matrix metalloproteinase (MMP); Mucous membrane pemphigoid (MMP)
- MMPs. *See* Matrix metalloproteinases (MMPs) and ameloblastomas
- MNTI. *See* Melanotic neuroectodermal tumor of infancy (MNTI)
- Moderate dysplasia, 269
- Mohs surgery, 1495, 1504, 1510, 1511, 1519
- Molecular genetic data
ALK+ anaplastic large cell lymphoma, 1067–1068
Burkitt lymphoma, 1056–1057
classical Hodgkin lymphoma, 1035
DLBCL, 1041
extramedullary plasmacytoma, 1057
extranodal NK/T-cell lymphoma, 1061–1062
of hyaline-vascular Castleman disease, 1021
MALT lymphoma, 1055–1056
mantle cell lymphoma, 1053
nodular lymphocyte-predominant Hodgkin lymphoma, 1037
- Molecular-genetic data
ITAC, 386
malignant melanomas, 393
nasopharyngeal carcinomas, 398–399
- Molecular genetic data, follicular lymphoma, 1049
- Moll's gland cyst. *See* Hidrocystomas
- Molluscum contagiosum, 1684–1685
- Monocytoid B cells, 999
- Mononucleosis, 1355
- Monophasic synovial sarcoma. *See* Synovial sarcoma
- Monosodium urate crystals, in gout, 953
- Monospot test, 1666
- Monostotic fibrous dysplasia, 964–965
- MPA. *See* Microscopic polyangiitis
- MPNST. *See* Malignant peripheral nerve sheath tumor (MPNST)
- MPO. *See* Myeloperoxidase
- MRI. *See also* Magnet resonance imaging (MRI)
acute suppurative osteomyelitis, 958
chondrosarcoma, 977
chordoma, 980
chronic suppurative osteomyelitis, 959
gout, 953
osteoblastoma, 969
parosteal osteosarcoma, 973
PVNS, 956
- MRT. *See* Malignant rhabdoid tumor (MRT)
- MTC. *See* Medullary thyroid carcinoma (MTC); Medullary thyroid carcinoma (MTC)
- MT1-MMP. *See* Membrane type 1-matrix metalloproteinase (MT1-MMP) and ameloblastomas
- Mucinous adenocarcinoma, 572
- Mucinous carcinoma, 100
- Mucocoeles, 74, 356–357
- Mucocoeles, of salivary gland, 480–481
- Mucoepidermoid carcinoma, 546–552
- Mucoepidermoid carcinoma (MEC), 1352, 1412
- Mucoepidermoid carcinomas (MEC), 17, 23, 102, 169, 391
- Mucorales
clinical presentation, 1636
etiology, 1635–1636
histopathology, 1636–1637
serology, 1637
treatment, 1637
- Mucor hyphae, 1637
- Mucormycosis, 1637
- Mucosa-associated lymphoid tissue (MALT) lymphoma. *See also* Extranodal marginal zone B-cell lymphoma
clinical features, 1054
of conjunctiva, 1105
differential diagnosis, 1056
immunohistochemistry, 1055
of lacrimal gland, 1106

- [Mucosa-associated lymphoid tissue (MALT)]
 large cell transformation in, 1055
 lymphoepithelial sialadenitis *versus*, 1100
 molecular genetic data, 1055–1056
 of orbit, 1105
 immunostaining, 1108
 pathology, 1054–1555
 of salivary glands, 1094–1095
 of skin, 1111
 of thyroid, 1102, 1103
 in situ hybridization for
 immunoglobulin mRNA, 1104
 of tonsil, 1091
 treatment and prognosis, 1056
- Mucosal neuromas, 692–694
- Mucosal surfaces, 101
- Mucosal ulcerations, 1657
- Mucoserous (salivary) glands,
 hamartomas, 361
- Mucous cell metaplasia, 1207
- Mucous membrane pemphigoid (MMP),
 243, 249–251
 clinical presentation, 249–250
 diagnosis, 251
 immunology, 251
 immunopathology, 250–251
 pathology, 250
 treatment, 251
- Mucous retention cysts, 59
 antrochoanal polyp with, 351
- Mucus, allergic, 354–356
- Mucus-propelling cilia, 351–352
- Muir-Torre syndrome, 1488, 1489, 1493, 1553
- Multicentric Castleman disease, 1009
 clinical features, 1022
 pathology, 1023
- Multimodality therapy, for ONB, 732
- Multinodular goiter, 1390–1391
- Multiple endocrine neoplasia, 1437
- Multiple endocrine neoplasia (MEN), 1348
- Multiple endocrine neoplasia (MEN), 677, 692
- Multiple odontomas, 1253
- Multiple primary malignancies, 145
- Multiple syringomas, 1342
- Mumps, 495, 1687
- Murine double minute 2 (MDM2) and p14
 (ARF) expression in ameloblastomas,
 1211
- Murk Jansen's chondrodysplasia, 1458
- Myalgia, 252
- MYC gene translocation, DLBCL, 1041
- Mycobacterial cervical lymphadenitis,
 1624–1625
- Mycobacterial (tuberculous) lymphadenitis,
 1012
- Mycobacterium avium-intracellulare
 (MAI), 38
- Mycobacterium avium-intracellulare*
 (MAI), 1624
- Mycobacterium tuberculosis*, 1012
 clinical stages, 1621
 epidemiology, 1621
 in the head and neck, 1622
 laryngeal, 1622–1625
 mucocutaneous, 1622
 primary sinonasal tract, 1622
 reactivation, 1621–1622
- Mycoplasma pneumoniae*, 260
- Mycosis fungoides, 1069–1070
- Myeloid sarcoma, 1073
 of salivary glands, 1095
- Myeloperoxidase (MPO), 650
- MYH-associated polyposis, 1487
- Myoepithelial carcinoma, 580–583
- Myoepithelial carcinoma, 36
- Myoepithelial cells, 35
- Myoepithelioma, 519–522
 clinical features, 519
 defined, 519
 differential diagnosis, 521
 immunohistochemistry, 520–521
 pathology, 519–520
 treatment, 521–522
- Myofibroblastoma, 1152
- Myofibroma
 clinical features, 837
 differential diagnosis, 841–842
 electron microscopic findings, 840–841
 immunohistochemical findings, 840
 molecular findings, 840
 pathologic findings, 838–840
 prognosis and treatment, 842–843
 radiologic imaging, 837–838
- Myofibromatosis. *See* Infantile myofibroma
- Myofibromatosis-myofibroma, 1358
- Myogenic neoplasms, 1361
- Myosin heavy chain genes (MYH), 1487
- Myositis ossificans (MO) circumscripta
 clinical findings, 818–819
 differential diagnosis, 820
 electron microscopy, 820
 immunohistochemistry, 820
 pathologic findings, 819–820
 prognosis and treatment, 820
 radiologic imaging, 819
- Myospherulosis, 64, 358–359
- Myospherulosis, 1643–1644
- Myotonic dystrophy, 1480
- Myxofibrosarcoma, 886–887, 889
- Myxoid liposarcoma, 881, 882
- Myxoid liposarcomas, 58–59
- Myxoid malignant fibrous histiocytoma.
See Myxofibrosarcoma
- Myxoid neurothekeomas, 695
- Myxoid soft tissue sarcomas, 58–59
- Myxomas, 1279
 external auditory canal, 448–449
- MZL. *See* Marginal zone lymphoma (MZL)
- NARES. *See* Nonallergic rhinosinusitis with
 eosinophilia syndrome (NARES)
- Nasal biopsy, in ARS, 346
- Nasal cavity
 extranodal NK/T-cell lymphoma,
 1060–1064
 hematolymphoid neoplasms, 1081–1086
 lateralization of cancer of, 372
 metastases to, 402
 internal anatomy of, 373
 squamous cell carcinomas of, 371–374
- Nasal cavity sinuses, 63–68
 lesions, 64
 angiofibromas, 64
 myospherulosis, 64
 paranasal sinus mucocoeles, 64
 rhinoscleroma, 64
 sinonasal hemangiopericytoma, 64
- malignant lesions, 64–68
 heterotopia, of neuroglial tissue, 68
 nasopharyngeal carcinoma, 64–65
 olfactory neuroblastoma, 65–67
 paraganglioma, 67–68
 sinonasal adenocarcinoma, 67
 sinonasal neuroendocrine carcinoma, 67
 sinonasal undifferentiated carcinoma,
 66–67
- Nasal cerebral heterotopia, 1348–1349
- Nasal chondromesenchymal hamartoma
 (NCMH), 974–975, 1351
- Nasal encephalocele (NE)
 anatomy, 674–675
 clinical features, 675
- [Nasal encephalocele (NE)]
 diagnosis, 675–676
 imaging, 675
 overview, 674
 pathogenesis, 676
 pathology, 675
 treatment, 676
- Nasal glioma (NG), 1348
 clinical features, 671–672
 diagnosis, 673–674
 imaging, 672
 overview, 671
 pathogenesis, 674
 pathology, 672–673
 treatment, 674
- Nasal heterotopia. *See* Nasal glioma (NG)
- Nasal mucosa, 672
- Nasal obstruction, rhinosinusitis
 medicamentosa and, 347
- Nasal polyps, 348–350
 clinical features, 348
 with cystic fibrosis, 353
 pathology, 348–350
 with squamous metaplasia, 368
 treatment, 350
- Nasal septum, 953
 squamous cell carcinomas, 373–374
- Nasal vestibule
 squamous cell carcinomas, 372–373
 staging of carcinomas, 373
- Nasopharyngeal carcinoma (NPC), 47,
 64–65, 394–200, 1668–1669
 anatomy, 394–395
 classification of, 397
 clinical features, 395–396
 differential diagnosis, 399
 Epstein-Barr virus (EBV) genome
 detection in, 1355
 etiology, 395
 immunohistochemistry, 398
 molecular-genetic data, 398–399
 pathology, 396–398
 treatment and prognosis, 399–400
 undifferentiated nasopharyngeal
 nonkeratinizing carcinoma, 1357
 viral studies, 398
- Nasopharynx
 carcinomas. *See* Nasopharyngeal
 carcinomas
 hematolymphoid neoplasms, 1086–1088
 papillary adenocarcinomas, 400–402
 salivary-type neoplasms, 391
- National Cancer Institute (NCI), 1
- National Institute on Drug Abuse, 663
- Natural killer (NK) cells, 262
- NBCCS. *See* Nevoid BCC syndrome (NBCCS)
- NCI. *See* National Cancer Institute (NCI)
- NCMH. *See* Nasal chondromesenchymal
 hamartoma (NCMH)
- NE. *See* Nasal encephalocele (NE)
- NEC. *See* Neuroendocrine carcinomas (NEC)
- Neck dissections
 adjuvant chemotherapy, 1144–1145
 extended radical, 1136
 gross examination of
 radiologic examination, 1137
 technique, 1137–1138
 microscopic examination, 1138
 modified radical, 1136
 radical, 1136
 selective, 1136
 unexpected pathology
 granulomatous lesions, 1142
 lymph node heterotopias, 1142, 1143
 metastatic papillary thyroid
 carcinoma, 1142

- Necrobiosis with palisading mantle of histiocytes, 1367
- Necrosis, 1591
- Necrotizing external otitis, 427–428
- Necrotizing granulomatous lymphadenitis, 1354
- Necrotizing granulomatous nodules, 952
- Necrotizing sialometaplasia, 491–493
- Neisseria gonorrhea*, 953
- Neonatal hyperparathyroidism, 1458
- Neoplasm, in ocular adnexa, 74–75
cavernous hemangiomas, 74
hemangiopericytoma, 74
meningioma, 75
mucocles, 74
pilomatrixoma, 74
pleomorphic adenoma, 74–75
schwannoma, 75
- Neoplasms
of bone, hematolymphoid, 1108–1109
of eye, hematolymphoid, 1103–1105
of ocular adnexa, hematolymphoid, 1103–1105
of skin, hematolymphoid, 1109–1112
of thyroid, hematolymphoid, 1100–1101
- Neoplastic cells, 13, 661
- Neoplastic diseases, condroid. *See* Neoplastic diseases, osseous
- Neoplastic diseases, mesenchymal
aneurysmal bone cyst, 986–987
angiosarcoma, 982–983
desmoplastic fibroma, 987–988
eosinophilic granuloma, 989
epithelioid hemangioendothelioma, 981–982
Ewing's sarcoma, 989
fibrosarcoma, 988–989
giant cell granuloma, 984–985
giant cell tumor, 984
hemangioma, 981
hyperparathyroidism, 985–986
lymphangioma, 983–984
- Neoplastic diseases, nonchondroid. *See* Neoplastic diseases, mesenchymal
- Neoplastic diseases, nonosseous. *See* Neoplastic diseases, mesenchymal
- Neoplastic diseases, osseous
cartilaginous lesions, 974
chondroblastomas, 978–979
chondroid metaplasia, 975–976
chondroma, 976
chondromyxoid fibroma, 978
chondrosarcoma, 976–978
chordoma, 979–981
exostosis, 967
extraosseous osteosarcoma, 974
nasal chondromesenchymal hamartoma, 974–975
ossifying fibroma, 970–971
osteoblastoma, 969–970
osteochondroma, 968
osteoid osteoma, 968–969
osteosarcoma, 971–974
- Nephrolithiasis, 1455
- Nephrotic syndrome, 252
- Nerve sheath myxomas, 694
- Nestin antibodies
AFOD, 1251
AMF, 1244
and AOT, 1238
and ODOMYX, 1286
- Neurilemoma, 127–128
- Neuroblastoma (NB), 1347, 1355
- Neuroendocrine carcinomas (NEC), 322–323, 380. *See also* Primary small cell carcinoma
- Neuroendocrine differentiation, middle ear adenomas, 450–451
- Neuroendocrine tumors, 162–167
AC, 164–166
combined small cell neuroendocrine carcinoma, 167
overviews, 162
paraganglioma, 167
SCNEC, 166–167
TC, 162–164
- Neurofibroma, 63, 127–128, 681–683
- Neurofibromatosis 1, 687–689
- Neurofibromatosis 2, 689–691
- Neurofibromatosis (NF), 676, 1344
- Neurofibromatosis type 1 (NF1), 1601
- Neurofibrosarcoma. *See* Malignant peripheral nerve sheath tumor (MPNST)
- Neurogenic sarcoma. *See* Malignant peripheral nerve sheath tumor (MPNST)
- Neurothekeoma, 694–696
- Neutrophilic abscesses, 1493–1494
- Neutrophilic microabscess, 652, 653
- Nevoid BCC syndrome (NBCCS), 1344
- Nevus, 170
- Nevus sebaceous of Jadassohn (NSJ), 1341–1342
clinical features, 1536
differential diagnosis, 1537
imaging, 1536
molecular genetics, 1537
pathology, 1536–1537
treatment and prognosis, 1537–1538
- NF. *See* Neurofibromatosis (NF)
- NF-2
in acoustic neuroma, 454
in meningiomas, 456
- NG. *See* Nasal glioma (NG)
- NHL. *See* Non-Hodgkin's lymphoma (NHL)
- Nicotiana rustica*, 287
- Nicotiana tabacum*, 287
- Nicotinic stomatitis
clinical features, 208–209, 277–278
defined, 277
diagnosis, 278
pathology, 209, 278
treatment, 209, 278
- NIH diagnostic criteria, for NF1, 687
- Nikolsky sign, 250, 259
- NK. *See* Natural killer (NK) cells
- NK/T-cell lymphomas
clinical features, 660–661
immunohistochemistry, 662
pathology, 661
treatment and prospect, 662
- Nodal and extranodal lymphoma, 63
- Nodal marginal zone lymphoma, 1060
- Nodular BCC, 1496
- Nodular/diffuse dermal infiltrate diagnosis, of hematolymphoid lesions of skin, 1113–1114, 1115
- Nodular fasciitis, 54
in children, 1359
- Nodular fasciitis and related lesions
including cranial fasciitis, 812
clinical findings, 813
differential diagnosis, 813–815
electron microscopy, 813
imaging, 813
immunohistochemistry, 813
molecular findings, 813
pathologic findings, 813
prognosis and treatment, 815
- Nodular goiter, 4–5
- Nodular KS, 1660
- Nodular lymphocyte-predominant Hodgkin lymphomas, 1035–1039
clinical features, 1036
differential diagnosis, 1038–1039
immunohistochemistry, 1037
molecular genetic data of, 1037
pathology, 1036–1037
versus PTGC, 1005
transformation to non-Hodgkin lymphoma, 1037
treatment and prognosis, 1039
- Nodular melanoma, 1509
- Nodular sclerosis, classical Hodgkin lymphoma, 1032–1033
- Nodulosis—arthropathy—osteolysis syndrome, 1344
- Nonallergic rhinosinusitis with eosinophilia syndrome (NARES), 347
- Noncutaneous leiomyosarcoma, 876
- Nonepithelial larynx tumors, benign, 126–129
hemangioma, 126–127
leiomyoma, 128–129
lipoma, 128
neurilemoma, 127–128
neurofibroma, 127–128
overviews, 126
- Nonepithelial tumors, 63
- Non-Hodgkin lymphoma (NHL), 15, 39, 1039–1073, 1354
adult T-cell leukemia/lymphoma, 1072
anaplastic large cell lymphoma, 1065–1068
angioimmunoblastic T-cell lymphoma, 1064
in B-cell, 43–45
follicular lymphoma, 44–45
mantle cell lymphoma, 44
small lymphocytic lymphoma, 44
Burkitt lymphoma, 1056–1057
CLL/SLL, 1059
DLBCL, 1039–1045
extramedullary plasmacytoma, 1057–1059
extranodal NK/T-cell lymphoma, 1060–1064
FNA, 39
FNAB, 40–43
anaplastic large cell lymphoma, 42–43
Burkitt's lymphoma, 40–41
diffuse large B-cell lymphoma, 41–42
immunoblastic lymphomas, 42
lymphoblastic lymphoma, 40
follicular lymphoma, 1045–1051
hydroa vacciniforme-like lymphoma, 1072
immunodeficiency-associated lymphoproliferative disorders, 1072–1073
lymphoblastic leukemia/lymphoma, 1060
lymphoplasmacytic lymphoma, 1059–1060
MALT lymphoma, 1054–1056
mantle cell lymphoma, 1051–1054
mycosis fungoides, 1069–1070
nodal marginal zone lymphoma, 1060
peripheral T-cell lymphoma, 1064–1065
primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, 1071–1072
primary cutaneous CD4+ small/medium T-cell lymphoma, 1071
primary cutaneous CD30+ T-cell lymphoproliferative disorders, 1068–1069
Sézary syndrome, 1070–1071
subcutaneous panniculitis-like T-cell lymphoma, 1071

- Noniatrogenic hypoparathyroidism
clinical features, 1460
differential diagnosis, 1460
gene alterations in, 1461
molecular biology, 1461
pathologic features, 1460
treatment and prognosis, 1461
- Nonintestinal-type adenocarcinoma
(Non-ITAC), 387-389
- Nonkeratinizing carcinomas (NKC),
376-377
of nasopharynx, 397
- Nonkeratinizing squamous cell carcinomas,
305-308
immunohistochemistry, 307-308
microscopic features, 306-307
- Nonkeratinizing undifferentiated
carcinomas, 308-309
- Nonneoplastic bone diseases
cemento-osseous dysplasia, 965-966
cherubism, 966-967
cortical defects of mandible, 962-963
cranial fasciitis, 966
fibrous dysplasia, 964-965
focal osteoporotic bone marrow defect,
961-962
osteoarthritis, 958
osteomyelitis, 958-960
osteoradionecrosis, 960-961
Paget's disease, 963-964
relapsing polychondritis, 961
- Nonneoplastic disease, 3-6
- Nonneoplastic joint disease. *See*
Nonneoplastic bone disease
- Nonneoplastic lesions
acquired. *See* Acquired nonneoplastic
lesions
of ear and temporal bone, 425-432
classification, 425
- Nonneoplastic salivary gland lesions, 20-21
infiltration, fatty, 20
sialadenitis, 20-21
- Non-PTH-related hypercalcemia
clinical features, 1459
differential diagnosis, 1459
molecular biology, 1460
pathologic features, 1459
treatment and diagnosis, 1459-1460
- Nonspecific reactive lymphoid hyperplasia
lymph node, 997-1003
nasopharynx, 1087
of ocular adnexa, 1106-1107
of oral cavity and oropharynx, 1091
- Nonsteroidal anti-inflammatory drugs, 260
- Nonsuppurative osteomyelitis. *See* Chronic
sclerosing osteomyelitis
- Noonan syndrome, 1523
- NSJ. *See* Nevus sebaceous of Jadassohn
(NSJ)
- Nuchal fibrocartilaginous pseudotumor
(NFP), 1728-1729
- Nuchal fibroma
clinical features, 846
differential diagnosis, 847
electron microscopy, 847
imaging, 846
immunohistochemistry, 847
pathology, 846-847
treatment and prognosis, 847
- Nuchal-type fibroma
clinical features, 1514
differential diagnosis, 1515
imaging studies, 1514
immunohistochemistry, 1514
pathology, 1514
treatment and prognosis, 1515
- Nuclear atypia, 7
- Nutritional deficiencies, oral cancer, 289
- OaCCOT. *See* Odontoma-associated
calcifying cystic odontogenic tumor
(OaCCOT)
- Obstructive sialadenitis, 485-486
- Obstructive sleep apnea, 226-227
clinical features, 227
pathology, 227
treatment, 227
- Occlusive phlebitis, 1390
- Occult primary
to cervical nodes
adenopathy site, 1147-1148
clinical data, 1147
diagnosis, 1150-1152
lymphatic region, of neck, 1147
lymph node biopsy, 1150
primary lesion search, 1148-1150
immunohistochemistry
primary tumor discovery, 1154
treatment, 1154-1155
- Ococyoma
clinical features, 530
defined, 530
differential diagnosis, 531
pathology, 530-531
treatment, 531
- Octreotide scintigraphy, for PGL, 718
- Ocular adnexa, 70-81
diagnosis, 71-72
hematolymphoid lesions of, 1103-1107
clinical features, 1104
diagnostic considerations, 1107
neoplasms, 1103-1105
reactive/inflammatory, 1105-1107
lesions, 72-74
malignant tumors, 75-79
ACC, 76
basal cell carcinomas, 75-76
Merkel cell tumor, 77
metastatic carcinoma, 78-79
orbital teratomas, 77
retinoblastoma, 77-78
sebaceous carcinoma, 76-77
squamous cell carcinoma, 76
melanocytic lesions, 79-81
malignant melanoma, 80-81
melanocytoma, 79-80
melanotic neuroectodermal tumor of
infancy, 79
neoplasm, 74-75
orbital cytology, 70
overviews, 70-72
- Ocular adnexal lymphoproliferative
disorders, 1599
- Oculodermal melanocytosis, 1560
- ODOMYX. *See* Odontogenic myxoma and
myxofibroma (ODOMYX)
- Odonto-ameloblastoma
clinical features, 1258-1259
etiology of, 1259
immunohistochemistry, 1260
radiographs, 1259
treatment and prognosis, 1260
- Odontogenic cysts, 69-70
- Odontogenic fibroma, 1276
- Odontogenic ghost cell lesions,
1260-1262
- Odontogenic keratocysts, 1344
- Odontogenic myxoma, 68-69
- Odontogenic myxoma and myxofibroma
(ODOMYX), 1283
age range and gender ratio, 1284
differential diagnosis, 1287-1288
etiology of, 1285
HRAS- and KRAS-encoded gene
products, 1287
immunohistochemistry
CK antibodies, 1286
- [Odontogenic myxoma and myxofibroma
(ODOMYX)]
[immunohistochemistry]
glycosaminoglycans, 1286
nestin and vimentin antibodies, 1286
molecular-genetic data, 1287
radiographic appearance of, 1284-1285
rate of growth, 1284
treatment and prognosis, 1288
ultrastructure of, 1287
- Odontogenic sarcomas
ameloblastic fibrodentino- and
fibro-odontosarcoma, 1310-1311
ameloblastic fibrosarcoma, 1307-1310
odontogenic fibrosarcoma, 1311-1312
odontogenic myxosarcoma, 1312-1313
- Odontomas
complex and compound odontomas,
1256-1258
complex odontoma (ODTx)
etiology, 1253-1255
imaging of, 1253
prevalence and incidence, 1252-1253
compound odontoma (ODTp)
etiology of, 1256
prevalence and incidents, 1255-1256
radiographs, 1256
odontoma-associated calcifying cystic
odontogenic tumor (OaCCOT), 1253
- Odynophagia, 243
- Oil red O stains, 77
- Olfactory neuroblastoma (ONB), 65-66,
65-67, 1363
clinical features, 728-729
diagnosis, 731-732
imaging, 729
immunohistochemistry, 731
overview, 728
pathology, 729-731
versus SNUC, 380
treatment, 731-733
ultrastructure, 731
- OLP. *See* Oral lichen planus (OLP)
- "On again-off again" symptoms, NARES, 347
- ONB. *See* Olfactory neuroblastoma (ONB);
Olfactory neuroblastoma (ONB)
- ONB vs ES/PNET, 732
- ONB vs SNUC, 732
- Oncocytic carcinoma, 573-574
- Oncocytic cysts, 117
- Oncocytic lesions, 168, 482-483
- Oncocytic neoplasms, 9
- Oncocytic schneiderian papilloma (OSP),
369-371
carcinomas and, 370-371
incidence of HPV in, 370
- Oncocytic tumors, 389-390
- Oncocytoma, 30
- Oncogenic viruses, ora cancer, 288
- Onion skinning. *See* Proliferative periostitis
- OPG. *See* Orbital paragangliomas (OPG);
Osteoprotegerin (OPG) and
osteoclastogenesis
- Ophthalmoscopy, 78
- Optic nerve glioma (juvenile pilocytic
astrocytoma), 1601-1602
- Optic nerve neoplasms, 1601-1602
- Oral cancer. *See also* Squamous cell carcinomas
altered immunity, 289
clinicopathologic consideration, 290
dental factors and chronic inflammation,
288-289
epidemiology/etiology, 385-389
risk factors, 386-389
incidence
in South Asia, 287
in United States, 286
molecular biology/genetics, 289-290

- [Oral cancer]
 nutritional deficiencies, 289
 TNM—staging system for, 291
- Oral candidiasis (OC), 1645
- Oral cavity, 59–63
 anatomy, 285
 developmental and/or congenital lesions, 1343
 hematolymphoid neoplasms, 1088–1094
 malignant oral lesions, 61–63
 mucocele of lip and ranulas, 1343
 oral lesions, 59–61
 overviews, 59
 squamous cell carcinomas of, 292–301
- Oral hairy leukoplakia, 210–211, 1669–1670
 clinical features, 210–211
 electron microscopy, 211
 pathology, 211
 treatment, 211
- Oral lesions, ulcerations, 59–61
- Oral lichen planus (OLP), 254
- Oral malignant melanomas, 323–326
 clinical features, 324
 pathology, 324–325
 treatment and prognosis, 325–326
- Oral melanocytic nevi, 203–204
- Oral radiation, 59
- Oral soft tissue metastases, 1156–1157
- Oral squamous cell carcinoma (OSCC), 267
- Oral submucous fibrosis (OSF), 278–279
- Oral tongue, squamous cell carcinomas, 295–298
- Orbit
 anatomy, 1595–1596
 extramedullary hematopoiesis in, 1027
 malformations
 dermoid cysts, 1596
 inflammation, 1598
 lymphatic malformation (lymphangioma), 1597–1598
 venous malformation (cavernous hemangioma), 1596–1597
 melanomas involving, 1603
 metastases to, 1603
 specimen handling, 1596
- Orbital cytology, 70
- Orbital meningiomas, 702
- Orbital paragangliomas (OPG), 724
- Orbital teratomas, 77
- Orbital tumors, 1728
- ORN. *See* Osteoradionecrosis (ORN)
- Orofacial TB, 1622
- Oropharyngeal cancer, TNM—staging system for, 292
- Oropharyngeal wall, squamous cell carcinomas, 303
- Oropharynx
 anatomy, 285
 hematolymphoid neoplasms, 1088–1094
 squamous cell carcinomas of, 301–305
- OSCC. *See* Oral squamous cell carcinoma (OSCC)
- OSF. *See* Oral submucous fibrosis (OSF)
- Osler-Rendu-Weber syndrome, 1523
- Osseous and cartilaginous choristomas
 clinical findings, 823
 differential diagnosis, 824
 imaging, 823
 immunohistochemistry, 824
 pathologic findings, 823
 prognosis and treatment, 822, 824
 radiologic imaging, 823
- Osseous labyrinth, 425
- Osseous metaplasia, of the retinal pigment epithelium (RPE), 1582
- Ossifying fibroma, 970–971
- Osteitis deformans. *See* Paget's disease
- Osteoarthritis, 958
- Osteoblastoma, 969–970
- Osteoblasts, 959, 965
- Osteochondroma, 968
- Osteoclasts, 959
- Osteoclasts-like giant cells, 979
- Osteoid, 972
- osteoma, 968–969
- Osteoma, 967
- Osteomyelitis, 958–960
- Osteonecrosis, 958
- Osteoprotegerin (OPG) and osteoclastogenesis, 1212
- Osteoradionecrosis (ORN)
 fibrosis, 961
 persistent carcinoma, 961
 radiation damages, 960
 treatment, 961
 wound-healing defect, 961
- Osteosarcoma, 57
 extragnathic, 972–973
 extraosseous, 974
 gnathic, 971–972
 paget's disease, 963, 974
 parosteal, 973
 radiation-associated, 974
 secondary, 974
 syndrome-associated, 974
 telangiectatic, 973–974
- Otic polyps, inflammatory, 431
- Otitis externa, 1611
- Otitis media, 428–429, 1611–1612
 in children, 958
- Otosclerosis, 444–445
- Overgrowth syndromes, 1344
- Owen, Sir Richard, 1429
- Oxalosis
 pathologic features, 954
 radiologic features, 954
- Oxyphil cells, of parathyroid glands, 1432–1433, 1435
- Oxyphilic adenomas, 1448
- Oxyphil-rich carcinomas, 1450
- PA. *See* Pleomorphic adenoma (PA)
- PABA. *See* Para-aminobenzoic acid (PABA)
- Paget's disease, 963–964
 of bone, 445
- Palatal cysts, 1343
- Palatine tonsils
 reactive follicular hyperplasia of, 1001–1003
 squamous cell carcinomas, 303–305
- Palpation thyroiditis, 1392
- PAN. *See* Polyarteritis nodosa
- Pancytokeratin, 973
- Paneth cells, in intestinal-type adenocarcinomas, 386
- Panhypopituitarism, 717
- PAP. *See* Prostate acid phosphatase (PAP)
- Papanicolaou Society of Cytopathology (PSC), 1
- Papanicolaou stain, 5, 33
- Papillary adenocarcinomas, nasopharynx, 400–402
 clinical features, 400–401
 differential diagnosis, 401–402
 immunohistochemistry, 401
 pathology, 401
 treatment and prognosis, 402
- Papillary carcinoma, 100
- Papillary cystadenocarcinoma (PCA), 29
- Papillary dermal fibrosis, 1476
- Papillary endothelial hyperplasia, 1357
 clinical features, 774
 differential diagnosis, 776
 immunohistochemistry, 776
 pathologic findings, 774–775
 prognosis and treatment, 776
 ultrastructure, 775
- Papillary keratosis. *See* Keratinized papilloma
- Papillary squamous carcinomas, 316–318
- Papillary squamous cell carcinoma (PSCC), 153–155
- Papillary thyroid carcinoma (PTC), 4, 9–11, 1352
 clinical features, 1393
 differential diagnosis, 1399–1400
 immunohistochemical markers, 1399
 lipomatous stroma with, 1399
 with nodular fasciitis like stroma, 1399
 pathology, 1393–1394
 RET/PTC rearrangement, genetic alteration in, 1399
 treatment and prognosis, 1400
 variants of, 11–13, 1395
 clear cell, 1399
 cribriform-morular, 1398–1399
 diffuse sclerosing, 1397
 follicular, 1396–1397
 oxyphilic (oncocytic/Hurthle cell), 1398
 solid, 1397–1398
 tall cell, 1397
 Warthin-like, 1398
- Papilliferous keratoameloblastoma, 1226–1227
- Papillomas, 119–124, 215–216, 1676
 clinical features, 215
 diagnosis, 215–216
 keratinized, 123–124
 nonkeratinized. *See* Recurrent respiratory papillomatosis (RRP)
 pathology, 215
 treatment, 216
- Papulomatosis, 1675–1677
- Para-aminobenzoic acid (PABA), 280
- Paracoccidioidomycosis, 1648
- Paracortex
 lymphoid cells in, 997
 reactive paracortical hyperplasia, 999–1000
- Paragangliomas (PGL), 67–68, 167
 CBPG, 718–721
 genetics, 718
 imaging, 717–718
 immunohistochemistry, 718
 JTPG, 721–722
 LPG, 723–724
 OPG, 724
 overview, 717
 pathology, 718
 SNPG, 724–725
 terminology, 717
 TPG, 725
 VPG, 722–723
- Paramyxoviral transcripts, in osteoclasts, 963
- Paranasal sinuses. *See also* Nasal cavity sinuses
 hematolymphoid neoplasms of, 1081–1086
 metastases to, 402
- Paranasal sinus mucoceles, 64
- Paraneoplastic pemphigus (PNP), 246–248
 diagnosis, 248
 immunology, 247–248
 immunopathology, 247
 pathology, 247
- Paraneurofibroma. *See* Diffuse neurofibroma (DNF)
- Parapharyngeal meningiomas, 702
- Parapharyngeal neurofibromas, 682
- Parathyroid aspirates, 1441

- Parathyroid cysts
clinical features, 1456
differential diagnosis, 1457
molecular biology, 1457
pathologic features, 1456–1457
treatment and prognosis, 1457
- Parathyroid embryogenesis, 1429
- Parathyroid glands, 19, 104–105
- Parathyroid glands, normal
anatomy, 1429–1430
microscopic, 1431–1433
ultrastructural, 1433
distribution of, 1430
embryology, 1429
fat surrounding, 1430
gross appearance, 1430
histochemistry/immunohistochemistry, 1433–1435
molecular biology, 1435
physiology and biochemistry, 1435–1437
receptors, 1435
stroma of, 1431
venous drainage, 1430
weight distribution, 1430
- Parathyroid hormone (PTH), 1429. *See also*
Primary hyperparathyroidism
action on renal tubular cells, 1436
analytic methods for, 1436–1437
- Parathyromatosis, 1454
- Parenchyma, 669
- Parenchymal cells, 669
- Parkes-Weber syndrome, 1523
- Parosteal osteosarcoma, 973
- PAS. *See* Periodic acid-Schiff (PAS); Periodic acid-Schiff (PAS)
- Patched (PTCH) gene underexpression in*
ameloblastomas, 1213
- Patch KS, 1660
- Pathogens, in infectious rhinosinusitis, 345
- Pathologic examination, in
hyperparathyroidism, 1443–1445
- Paul-Bunnell IgM test, 1666
- PBCD. *See* Posterior buccal cortical defect (PBCD)
- PCA. *See* Papillary cystadenocarcinoma (PCA)
- PCNA. *See* Proliferating cell nuclear antigen (PCNA)
- PCNA L.I. and calcifying odontogenic cyst (COC), 1265
- PCR studies, 40
- PD-ECGF/TP. *See* Thymidine phosphorylase (PD-ECGF/TP)
expression and stroma of
ameloblastomas
- PDS. *See* Pendred's syndrome (PDS)
- Pearly penile papule. *See* Fibrous papules (FPs)
- Pemphigoid, 248–250
bullous pemphigoid, 248–249
mucous membrane MMP, 249–251
- Pemphigus, 243–248
drug induced, 248
paraneoplastic pemphigus, 246–248
vegetans, 246
vulgaris, 243–246
- Pemphigus vegetans, 246
- Pemphigus vulgaris (PV), 59, 243–246
clinical presentation, 243–244
immunology, 246
immunopathology, 245–246
overviews, 243
pathology, 244–245
treatment, 246
- Pendred's syndrome (PDS), 1391
- Penicillins, 1621, 1691
- Penicillium marneffeii*, 1013
- Pentoxifyline, 1693
- PERAM. *See* Solid/multicystic ameloblastoma-peripheral (PERAM)
- Perchlorate antithyroid drugs, 1386
- Perineurioma, 696–698
- Periodic acid-Schiff (PAS), 60, 253, 670
- Peripheral eosinophilia, 658
- Peripheral nerves, 100
- Peripheral nerve sheath tumors
acoustic neuromas, 691–692
DNF, 686–687
GCT, 698–701
mucosal neuromas, 692–694
neurofibroma, 681–683
neurothekeoma, 694–696
NF1, 687–689
NF2, 689–691
perineurioma, 696–698
PNF, 683–686
schwannoma, 678–681
- Peripheral odontogenic fibroma (POF)
differential diagnosis, 1281
immunohistochemistry, 1281
local surgical excision, 1281
pathology, 1280–1281
prevalence and incidence, 1280
ultrastructure of, 1281
- Peripheral T-cell lymphoma, 1064–1065
- Peritonsillar abscess, 225, 1610
- Periungual fibroma. *See* Fibrous papules (FPs)
- PET. *See* Positron emission tomography (PET)
- PGL. *See* Paragangliomas (PGL)
- Phacoanaphylactic endophthalmitis, 73, 1576
- Phacolytic cells, 73
- Phaeohyphomycosis, 1639
- Phakomatous choristoma, 1367–1368
- Pharyngeal hypophysis, 708
- Pharyngoesophageal diverticulum (PED), 1720–1721
- Pharyngoesophageal (Zenker's) diverticulum
clinical features, 1720–1721
pathology, 1719–1720
treatment and prognosis, 1721
- Phenylbutazone antithyroid drugs, 1386
- Phenytoin, 217
therapeutic agents, 1344
- Phosphate-binding agents, 1456
- Phospho-retinoblastoma protein (pRb)
immunohistochemistry, 1453
- Phosphotungstic acid-hematoxylin (PTAH), 1433
- Photodynamic therapy, 275, 1488
- Phthisical eye, 1583
- Phthisis bulbi
clinical features, 1579
pathology, 1579–1582
- Pigmented congenital epulis. *See*
Melanocytic neuroectodermal tumor of infancy (MNTI)
- Pigmented hidrocystomas, 1485
- Pigmented villonodular synovitis (PVNS)
immunohistochemistry, 956–957
pathologic features, 956
radiologic features, 956
- Pilar cysts (PC), 1342
clinical features, 1477
differential diagnosis, 1478
electron microscopy, 1478
imaging studies, 1477
immunohistochemical studies, 1478
molecular-genetic data, 1478
pathology, 1477–1478
treatment and prognosis, 1478
- Pilomatricoma
clinical features, 1480
differential diagnosis, 1481
electron microscopy, 1480
imaging studies, 1480
immunohistochemistry, 1480
molecular genetic data, 1481
pathology, 1480
treatment and prognosis, 1481
- Pilomatricoma, 26, 74
from neck, 1342–1343
- Pinna, squamous cell carcinomas of, 460–462
- PIOSCC. *See* Primary intraosseous squamous cell carcinoma (PIOSCC)
- Piperacillin, 1612
- Pituitary adenomas
clinical features, 708–709
diagnosis, 712
imaging, 709–710
incidental, 709
overview, 708
pathogenesis, 714
pathology, 710–712
treatment, 712–713
- Pituitary carcinoma, 713
- Pituitary gland, 708
- Plasmablastic lymphoma, 1042–1042
- Plasma cells, 952
- Plasmacytoma, 1108
extramedullary, 1057–1059
- Platelet-derived growth factor (PDG)
expression and stroma of
ameloblastomas, 1211–1212
- PLCD. *See* Posterior lingual cortical defect (PLCD)
- Pleomorphic adenoma (PA), 33–37, 74–75, 168, 389, 511–519, 1722
cellular PA, 34–35
clinical features, 512–513
differential diagnosis, 518–519
hyaline PA, 35–36
immunohistochemistry, 517–518
myoepithelioma, 36
pathology, 513–517
spindle cell lesions, 35
vs. low grade malignancies, 36–37
- Pleomorphic cells, 28
- Pleomorphic liposarcoma, 884
- Pleomorphic RMS, 869, 873
- Pleomorphic sarcoma NOS. *See* Storiform pleomorphic malignant fibrous histiocytoma
- Pleomorphic sarcomas, 57
- Plexiform neurofibroma (PNF), 677, 683–686, 1363
and parotid gland, 1365
- Plexiform schwannomas, 680
- PLGA. *See* Polymorphous low-grade adenocarcinoma (PLGA)
- Plummer-Vinson syndrome (PVS), 175
- PMML. *See* Malignant melanomas
- Pneumocystis carinii*, 430
- Pneumocystosis, 1658–1659
- Pneumonia, interstitial giant cell pneumonia, 1685
- PNF. *See* Plexiform neurofibroma (PNF)
- Podoplanin, immunohistochemical stain, 984
- POF. *See* Peripheral odontogenic fibroma (POF)
- Polyarteritis nodosa (PAN), 655, 656–657
clinical features, 656–657
pathology, 657
treatment and prospect, 657
- Polychondritis, relapsing, 440–442
- Polyclonal carcinoembryonic antigen (CEA)
immunoreactivity, 1386

- Polycystic disease, of salivary glands, 478
 Polygonal cell sarcomas, 55–56
 Polyhydramnios, 1364–1365
 Polymethylmethacrylate (PMMA), 1576
 Polymicrobial infections, 958
 Polymorphous low-grade adenocarcinoma, 557–561
 Polymorphous low-grade adenocarcinoma (PLGA), 26, 27, 63
 Polyostotic fibrous dysplasia, 965
 Polypoid nasal mass, 672
 Pompe disease, 1392
 Poorly differentiated carcinoma
 clinical features, 1406
 pathology, 1406
 TP53 and *BRAF* mutations, 1407
 treatment and prognosis, 1407
 Positron emission tomography (PET), 1
 Postcricoid carcinoma, 176–177
 Posterior buccal cortical defect (PBCD), 963
 Posterior hypopharyngeal wall carcinoma, 176
 Posterior lingual cortical defect (PLCD), 962–963
 Postpartum thyroiditis, 1389
 Posttransplant lymphoproliferative disorders, 1073, 1667
 Postvaccination fatal disseminated infection, 1686
 Potassium iodide, 1638
 Pouch-derived cysts, 1457
 P53 protein
 and AOT, 1238
 p53 mutations in ameloblastomas, 1211
 PR. *See* Progesterone receptor (PR)
 PR3. *See* Proteinase 3
 Prasad's microstaging, mucosal malignant melanomas, 394
 Precancerous keratosis. *See* Actinic keratoses (AKs)
 Pregnancy, rhinosinusitis during, 347
 Primary acquired melanosis, 1561
 Primary bone lymphoma, 1108–1109
 Primary ciliary dyskinesia (PCD), 351–352
 Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, 1071–1072
 Primary cutaneous CD4+ small/medium T-cell lymphoma, 1071
 Primary cutaneous CD30+ T-cell lymphoproliferative disorders, 1068–1069
 Primary cutaneous DLBCL, leg-type, 1110–1111
 Primary cutaneous follicle center lymphoma, 1050, 1109–1110
 Primary cutaneous MALT lymphoma, 1111
 Primary effusion lymphoma, 1044
 Primary follicular lymphoma of thyroid, 1101
 Primary herpetic stomatitis, 59
 Primary hyperparathyroidism
 clinical differential diagnosis, 1438
 clinical presentation, 1438–1439
 definition, 1437
 epidemiology, 1437–1438
 FNA cytology, 1440–1442
 imaging studies, 1439–1440
 preoperative localization, 1439–1442
 selective venous sampling (SVS) for PTH levels, 1440
 treatment and prognosis, 1455–1456
 Primary intraosseous squamous cell carcinoma (PIOSCC), 1235, 1297
 frequency, 1298
 histomorphology of, 1298
 immunohistochemistry, 1299
 [Primary intraosseous squamous cell carcinoma (PIOSCC)]
 molecular-genetic data, 1299
 radiograms, 1298
 treatment and prognosis, 1299
 Primary lymphomas and plasmacytomas, 1414–1415
 Primary malignant melanoma of the larynx (PMML). *See* Malignant melanomas
 Primary oral CD30+ T-cell lymphoproliferative disorders, 1069
 Primary small cell carcinoma, 25–26
 Primary systemic amyloidosis, 1391
 Priming, 649
 Primitive neuroectodermal tumors (PNET), 1503
 Procainamide, 252
 Progesterone receptor (PR), 31
 Progressive transformation of germinal centers (PTGC), 1004–1005
 Proliferating cell nuclear antigen (PCNA), 697
 Proliferating follicular-cystic neoplasm. *See* Proliferating pilar cyst (PPC)
 Proliferating pilar cyst (PPC)
 clinical features, 1478
 differential diagnosis, 1479
 genetic association, 1479
 imaging studies, 1478
 immunohistochemical studies, 1479
 pathology, 1478–1479
 treatment and prognosis, 1479
 Proliferating tricholemmal cyst. *See* Proliferating pilar cyst (PPC)
 Proliferative myositis, 54
 Proliferative myositis/fasciitis and atypical decubital fibroplasia (ischemic fasciitis)
 differential diagnosis, 817–818
 electron microscopy, 817
 immunohistochemistry, 816
 molecular, 817
 pathologic findings, 816
 prognosis and treatment, 818
 radiologic imaging, 815–816
 Proliferative periostitis, 960
 Proliferative verrucous leukoplakia (PVL), 275
 Proptosis, 1596
 Propylthiouracil antithyroid drugs, 1386
 Prosecretory granules, 1433
 Prostate acid phosphatase (PAP), 31
 Prostate-specific antigen (PSA), 31
 Proteinase 3 (PR3), 650
 Proteus syndrome, 1523
 Pruritus, 248
 Prussak's space, 436
 PSA. *See* Prostate-specific antigen (PSA)
 Psammoma bodies, 10
 PSC. *See* Papanicolaou Society of Cytopathology (PSC)
 PSCC. *See* Papillary squamous cell carcinoma (PSCC)
 Pseudoallescheriasis, 1637–1638
 Pseudoepitheliomatous hyperplasia, 1345
 Pseudogout, 442–443. *See also* Calcium pyrophosphate crystal deposition disease (CPCDD)
 Pseudohyperparathyroidism
 clinical features, 1460
 differential diagnosis, 1460
 gene alterations in, 1461
 molecular biology, 1461
 pathologic features, 1460
 treatment and prognosis, 1461
 Pseudolymphoma, cutaneous, 1112
Pseudomonas aeruginosa, 1609
 Pseudophakia, 1565–1566
 Pseudovasculitis, 660
 Psoralen and ultraviolet light A (PUVA), 257
 Pterygium, 1573–1574
 PTGC. *See* Progressive transformation of germinal centers (PTGC)
 PT stage grouping, 98
 Pulmonary cryptococcosis, 1652
 Pulsion diverticula, 1720
 PUVA. *See* Psoralen and ultraviolet light A (PUVA)
 PV. *See* Pemphigus vulgaris (PV)
 PVL. *See* Proliferative verrucous leukoplakia (PVL)
 PVNS. *See* Pigmented villonodular synovitis (PVNS)
 Pyogenic bacterial infections, 1013
 Pyogenic granuloma. *See* Lobular capillary hemangioma; Lobular capillary hemangioma (LCH)
 Pyriform sinus carcinoma, 175–176
 Pymethamine, 1689
 QPTH. *See* Quick parathyroid hormone (QPTH)
 QuantiFERON-TB Gold, 1623
 Quick parathyroid hormone (QPTH), 104
 Quinidine, 252
 Quinolones, 1691
 Radiation-associated osteosarcomas, 974
 Radiation therapy, 14, 31, 976
 Radiography, FD, 964
 RANKL. *See* Receptor activator of nuclear factor- κ B ligand (RANKL) and osteoclastogenesis
 RAS. *See* Recurrent aphthous stomatitis (RAS)
 RCC. *See* Renal cell carcinoma (RCC)
 Reactive follicular hyperplasia, 997–999
 versus follicular lymphoma, 1051
 monocytoid B cells in, 999
 of palatine tonsils, 1001–1003
 Reactive/inflammatory hematomalymphoid lesions
 of eyes and ocular adnexa, 1105–1107
 of skin, 1112–1113
 of thyroid, 1101–1102
 Reactive lymphoid hyperplasia, 49–50
 of extranodal sites, 1001
 nonspecific, 997–1003
 specific, 1003–1029
 of tonsil, 1002, 1003
 Reactive paracortical hyperplasia, 999–1000
 Reactive periostitis, BPOP, and turret exostosis
 clinical findings, 818
 differential diagnosis, 818
 immunohistochemistry, 818
 pathologic findings, 818
 prognosis and treatment, 818
 radiologic imaging, 818
 Receptor activator of nuclear factor- κ B ligand (RANKL) and osteoclastogenesis, 1212
 Recurrent aphthous stomatitis (RAS), 261–263
 diagnosis, 262
 etiology, 261
 immunopathology, 262
 pathology, 262
 treatment, 263
 Recurrent laryngeal nerve paralysis, 1721
 Recurrent parotitis, 494–495

- Recurrent respiratory papillomatosis (RRP), 119–123
 clinical features, 120
 etiology, 119–120
 immunohistochemistry, 122
 molecular-genetic data, 122
 pathology, 121–122
 terminology, 119
 treatment, 122–123
- Reed-Sternberg cells, 44
 classical Hodgkin lymphoma, 1032–1035
 in cytomegalovirus lymphadenitis, 1008
 in infectious mononucleosis, 1007
 in Kimura disease, 1018
- Regaud type, 1355
- Reiter's syndrome, 261
- Relapsing polychondritis, 440–442, 961
 ANCA titers in, 441
- Renal cell carcinoma (RCC), 9, 16, 1459, 1729
- Renal cell-like sinonasal adenocarcinoma (RCSA), 1729
- Renal disease, 253
- Resection margins, 144
- Respiratory epithelial adenomatoid hamartomas, 360–361
- Retention cyst, 21
- Retina
 anatomy, 1591
 retinoblastoma, 1592–1595
 specimen handling, 1592
- Retinal anlage tumor. *See* Melanocytic neuroectodermal tumor of infancy (MNTI)
- Retinal pigment epithelium (RPE), 1580
- Retinoblastoma, 77–78
 clinical features, 1592–1593
 pathology, 1593–1594
 treatment, 1594
- Retinoblastoma* (RB) tumor suppressor gene in ameloblastomas, 1211
- Retinocytoma, 1594
- Retinoids, 1678
- Retromolar trigone (RMT), squamous cell carcinomas, 301–302
- Rhabdoid meningioma, 706
- Rhabdomyoblasts, 726
 in malignant triton tumor, 893
- Rhabdomyoma, 54, 60
 clinical features, 798–799
 differential diagnosis, 801–802
 imaging, 799
 immunohistochemistry, 800–801
 molecular findings, 801
 pathology, 799–800
 treatment and prognosis, 802
- Rhabdomyomatous mesenchymal hamartoma, 1362
- Rhabdomyosarcoma (RMS), 869–876, 1603
 nasal polyps, 349–350
- Rheumatoid arthritis, 1013–1014
 ear, 953
 larynx, 953
 nasal septum, 953
 pathologic features, 952–953
 temporomandibular joint, 953
- Rhinophyma
 clinical features, 1532–1533
 defined, 1532
 differential diagnosis, 1533
 immunohistochemistry, 1533
 molecular genetics, 1533
 pathology, 1533
 treatment and prognosis, 1533–1534
- Rhinoscleroma, 64, 1691
 clinical features, 1619
 clinicopathological stages, 1619
 differential diagnosis, 1620
- [Rhinoscleroma]
 epidemiology, 1618–1619
 histopathology, 1619–1620
 immunological considerations, 1619
 nasal cavity, 1085
 treatment, 1620
- Rhinosinusitis, 343
 in adults, classification, 344
 allergic, 343–345
 atrophic. *See* Atrophic rhinosinusitis (ARS)
 complications, 343–348
 factitial, 348
 idiopathic, 348
 infectious, 345
 occupational-environmental, 347
 pathology, 343
 during pregnancy, 347
 signs and symptoms, 344
 structural-mechanical, 347
 systemic causes, 348
 vasomotor, 345–346
- Rhinosinusitis medicamentosa, 347
- Rhinopodiosis, 1642–1643
- Rhizopus, 1637
- Riedel thyroiditis, 1388–1390
- Rifampin, 1627
- Rituximab, for DLBCL, 1045
- RMS. *See* Rhabdomyosarcoma (RMS)
- RMT. *See* Retromolar trigone (RMT)
- Robinson type lesion, 1484
- Romanowsky-type stains, 41
- Rosacea
 clinical features, 1532–1533
 defined, 1532
 differential diagnosis, 1533
 immunohistochemistry, 1533
 molecular genetics, 1533
 pathology, 1533
 treatment and prognosis, 1533–1534
- Rosai-Dorfman disease, 51–52, 439, 1023–1024. *See also* Sinus, histiocytosis with lymphadenopathy
 of nasal cavity, 1083–1085
 of skin, 1113, 1114
- Round cell liposarcoma, 881, 882
- Round cell sarcomas, 54–55
- Rovamycin, 1689
- RRP. *See* Recurrent respiratory papillomatosis (RRP)
- Rudimentary lumen formation, 865
- Rudimentary meningocele, 1349–1350
- Sabin Feldman Dye test, 1688
- Saccular cysts, 116
- Sac papillary tumor, endolymphatic, 457–458
- Saksenea vasoformis, 1638
- Salivary duct carcinoma (SDC), 28–29, 574–578
- Salivary duct cysts, 481
- Salivary gland anlage tumor, 1350
- Salivary gland heterotopias, 1352
Bartonella henselae causative organism, 1354
 mycobacterial and Bartonella (cat scratch disease) infection, 1353
- Salivary gland neoplasm
 with basaloid cell, 23–26
 adenoid cystic carcinoma, 24–25
 basal cell adenocarcinoma, 25
 basal cell adenoma, 23–24
 pilomatricoma, 26
 primary small cell carcinoma, 25–26
 challenges, diagnosis, 22–23
 by large cells, 28–32
 acinic cell carcinoma, 29–30
 clear cell change, 31–32
 high-grade MEC, 28
- [Salivary gland neoplasm]
 [by large cells]
 metastatic malignancies, 31
 oncocytoma, 30
 radiation therapy, 31
 salivary duct carcinoma, 28–29
 Warthin tumor, 30–31
- Salivary glands, 20–37, 101–103
 aplasia, 476–477
 choristomas, 427
 cystic fibrosis, 478–479
 cystic lesions, 21–22
 cysts
 LEC, 481–482
 mucocoeles, 480–481
 salivary duct cysts, 481
 functional unit, 475
 hematolymphoid neoplasms, 1094–1099
 heterotopia, 477–478
 HIV-associated lymphoid hyperplasia in, 1010
 hyperplasia, 500
 infiltrations
 amyloidosis, 484
 iron deposition, 484
 lipomatosis, 482
 oncocytic lesions, 482–483
 lesions, 63
 nonneoplastic salivary gland lesions, 20–21
 parotid gland, 475
 sebaceous glands, 475, 479–480
 sialadenitis. *See* Sialadenitis
 submandibular gland, 475–476
 tumors. *See* Tumors
- Salivary gland tumors, 26–28, 70
 lesions containing squamous cells, 27–28
 low-grade MEC, 26
 in lymphocytes, 32–33
 polymorphous low-grade adenocarcinoma, 27
- Salivary gland-type neoplasms, 167–170
 adenoid cystic carcinoma (ACC), 168–169
 mucoepidermoid carcinoma (MEC), 169
 oncocytic lesions, 168
 overviews, 167–168
 pleomorphic adenoma, 168
- Salivary-type neoplasms, 389–391
- Samter's triad, 346–347
- Sarcoid granulomas, 1693
- Sarcoidosis, 50, 73, 1354, 1438
 causes, 1692–1693
 clinical features, 1691–1692
 diagnosis, 1693
 histopathology, 1693
 predispositions, 1691
 treatment, 1693
- Sarcomas, 52–59, 63
 ancillary studies, diagnosis, 53–54
 of larynx, 173–174
 overviews, 52–53
 soft tissue lesions, 54
 soft tissue sarcomas, in head and neck region, 54–59
- Sarcomatoid carcinoma. *See* Spindlecell carcinomas (SPCC)
- Sarcomatoid SCC, 1492
- SCC. *See* Squamous cell carcinoma (SCC)
- Schistosoma, 1638
- Schneiderian mucosa, 1609
- Schneiderian papillomas, 361–371
 exophytic papillomas, 362–363
 frequency of, 362
 inverted papilloma. *See* Inverted papilloma
 oncocytic schneiderian papilloma (OSP), 369–371
- Schopf-Schulz-Passarge syndrome, 1484
- Schwann cells, 678

- Schwannoma, 75, 678–681, 1363–1365
 SCLE. *See* Subacute cutaneous lupus erythematosus (SCLE)
 Sclerosing epithelioid fibrosarcoma, 886, 887
 Sclerosing mucoepidermoid carcinoma with eosinophilia, 1412
 Sclerosing polycystic adenosis, 497–499
 Sclerosing sweat duct carcinoma. *See* Microcystic adnexal carcinoma (MAC)
 Sclerosing type BCC, 1496
 SCNEC. *See* Small cell neuroendocrine carcinomas (SCNEC)
 Scrofula, 1623
 SDC. *See* Salivary duct carcinoma (SDC)
 Sebaceous adenoma (SA), 32, 532–533, 1554
 clinical features, 1488
 differential diagnosis, 1489
 immunohistochemistry, 1489
 molecular genetics, 1489
 pathology, 1488
 treatment and prognosis, 1489
 Sebaceous carcinoma, 32, 76–77, 567–568, 1554–1556
 Sebaceous differentiation, of salivary glands, 479–480
 Sebaceous hyperplasia (SH), 1482
 clinical features, 1487
 differential diagnosis, 1488
 immunohistochemistry, 1487
 molecular genetics, 1487–1488
 pathology, 1487
 treatment and prognosis, 1488
 Sebaceous lymphadenocarcinoma, 568
 Sebaceous trichofolliculoma, 1488
 Seborrheic keratoses (SK)
 associated syndromes, 1477
 clinical features, 1475
 differential diagnosis, 1476–1477
 imaging studies of, 1475
 immunohistochemical studies, 1475
 treatment and prognosis, 1477
 Secondary (dedifferentiated) AMCA, 1295
 etiology of, 1296
 histochemical study, 1296
 molecular-genetic data, 1296
 radical surgical resection, 1296
 Secondary (dedifferentiated) peripheral (arising in preexisting benign ameloblastoma), 1296
 clinical features, 1297
 differential diagnosis, 1297
 etiology of, 1297
 radiographs, 1297
 treatment and prognosis, 1297
 Secondary hyperparathyroidism
 clinical presentation, 1442
 definition, 1442
 epidemiology, 1442
 imaging studies, 1442–1443
 preoperative localization, 1442–1443
 selective venous sampling, 1443
 treatment and prognosis
 standard medical therapy, 1456
 surgical management, 1456
 Secondary malignancies, of eyes, 1603
 Secondary osteosarcoma, 974
 Secretory meningioma, 705
 Selective neck dissection (SND), 1135
 Senile keratosis. *See* Actinic keratoses (AKs)
 Sentinel lymph node (SLN), 101, 1137
 Serous otitis media (otitis media with effusion), 1612
 Serum calcitonin analysis, 1150
 SETTLE. *See* Spindle epithelial tumor with thymus-like differentiation (SETTLE)
 Severe chronic active EBV infection, 1667
 Severe dysplasia, 269
 Sézary syndrome, 1070–1071
 Sheathlin and calcifying odontogenic cyst (COC), 1265
 Short tau inversion recovery (STIR) sequences, 1518
 Sialadenitis, 20–21
 acute suppurative sialadenitis, 484–485
 cheilitis glandularis, 490–491
 chronic, 21, 33
 chronic sclerosing sialadenitis, 486–489
 cytomegalovirus, 495–497
 mumps, 495
 necrotizing sialometaplasia, 491–493
 obstructive sialadenitis, 485–486
 radiation sialadenitis, 489–490
 recurrent parotitis, 494–495
 subacute necrotizing sialadenitis, 493
 Sialoadenitis, chronic, 102
 Sialoblastoma, 595–596
 Sialometaplasia, 102
 Sialosis, 20, 499–500
 Sincipital encephaloceles, 674
 Sinonasal adenocarcinoma, 67
 Sinonasal fungal disease
 alternaria, 1640
 aspergillosis, 1629–1632
 bipolaris and exserohilum, 1639–1640
 blastomycosis, 1642
 cladosporium, 1640–1641
 clinicopathological classifications, 1628–1629
 cryptococcosis, 1642
 curvularia, 1640
 fungus ball/mycetoma, 1632–1634
 hyalohyphomycosis, 1641
 mucormycosis and
 entomophthoromycosis, 1634–1637
 myospherulosis, 1643–1644
 phaeohyphomycosis, 1639
 pseudoallescheriasis, 1637–1638
 rhinosporidiosis, 1642–1643
 sporotrichosis, 1641–1642
 Sinonasal hemangiopericytoma, 64
 clinical features, 850
 immunohistochemistry, 850
 molecular findings, 850
 pathology, 850
 treatment and prognosis, 850
 Sinonasal leiomyosarcoma, 876
 Sinonasal neuroendocrine carcinoma, 67
 Sinonasal NK/T-Cell lymphoma, 1670–1671
 Sinonasal paragangliomas (SNPG), 724–725
 Sinonasal polyposis, 1610
 Sinonasal polyps, 674
 Sinonasal tumors, cytokeratin expression, 379
 Sinonasal undifferentiated carcinoma (SNUC), 731
 Sinonasal undifferentiated carcinomas (SNUC), 66–67, 377–380
 histogenesis, 378
 Sinuses, 1351
 histiocytosis with lymphadenopathy, 1415
 vascular transformation of, 1005–1006
 Sinus histiocytosis, 1000–1001
 with massive lymphadenopathy, 1023–1024
 Sinusitis
 acute bacterial, 345
 chronic, 345
 Sjögren's syndrome, 32, 1014, 1660
 SJS. *See* Stevens–Johnson syndrome (SJS)
 Skeletal muscle hemangioma, 1356
 Skin
 epidermal and cutaneous adnexal lesions, 1341–1342
 [Skin]
 hematolymphoid lesions of, 1109–1115
 diagnostic considerations, 1113–1115
 neoplasms, 1109–1112
 reactive/inflammatory, 1112–1113
 pigmented lesions, 1339–1341
 tag, 1352. *See also* Branchial cleft cyst
 Skull meningioma, 703
 SLE. *See* Systemic lupus erythematosus (SLE)
 SLL. *See* Small lymphocytic lymphoma (SLL)
 SLN. *See* Sentinel lymph node (SLN)
 Small cell carcinoma, 589–591
 Small cell/mixed cell infiltrates
 diagnosis, of hematolymphoid lesions of skin, 1114–1115
 Small cell neuroendocrine carcinomas (SCNEC), 166–167, 380–382
 versus SNUC, 380
 Small lymphocytic lymphoma (SLL), 33, 44
 Smith type lesion, 1484
 Smokeless tobacco keratosis, 280–281
 clinical features, 280–281
 defined, 280
 diagnosis, 281
 pathology, 281
 treatment, 281
 Smoking, oral cancer, 286–288
 SND. *See* Selective neck dissection
 SNPG. *See* Sinonasal paragangliomas (SNPG)
 SNUC. *See* Sinonasal undifferentiated carcinoma (SNUC); Sinonasal undifferentiated carcinomas (SNUC)
 Soft palate, squamous cell carcinomas, 302–303
 Soft tissues
 developmental cysts of neck, 1351
 lesions, 54
 lymph node(s), 1353–1355
 metastases, 1140
 neoplasms, 1603
 perineurioma, 697
 tumors and, 1355–1367
 like lesions of, 1367
 Soft tissue sarcomas, in head and neck region, 54–59
 Ewing's sarcoma, 55
 leiomyosarcomas, 58
 myxoid soft tissue sarcomas, 58–59
 osteosarcomas, 57
 pleomorphic sarcomas, 57
 polygonal cell sarcomas, 55–56
 round cell sarcomas, 54–55
 spindle cell sarcomas, 58
 synovial sarcomas, 56–57
 Soft tissue tumors, of salivary gland, 598–600
 juvenile hemangioma, 600–601
 sialolipoma, 601–603
 SOHLs. *See* Squamous odontogenic hamartoid lesions (SOHLs)
 Solar elastosis, 1489
 Solar keratosis. *See* Actinic keratoses (AKs)
 Solid cell nests in thyroid, 1386
 Solid/multicystic ameloblastoma–central
 etiology of
 basaloid pattern, 1206–1207
 plexiform growth pattern, 1205
 immunohistochemistry
 basement-type heparan sulfate proteoglycan (HSPG), 1209
 cell proliferation markers, 1209
 CKs and vimentin, 1208
 collagen types, 1208–1209
 extracellular matrix proteins and basement membrane, 1208

- [Solid/multicystic ameloblastoma–central]
[immunohistochemistry]
 integrin, 1209
 laminin, 1208
 mitogen-activated protein kinases (MAPKs), roles of, 1209
 tenascin, 1208
prevalence and incidence
 age range, 1203
 frequency of, 1202–1203
 location of, 1203
 plexiform growth pattern, 1204
 radiological appearance and, 1204
- Solid/multicystic ameloblastoma–peripheral (PERAM)
 CK-19 and Ber-EP4, 1217
 differential diagnosis, 1217
 gender distribution of, 1215
 immunohistochemical studies, 1216–1217
 molecular-genetic data, 1217
 pathology, 1216
 prevalence and incidence, 1215
 radiological changes, 1216
 treatment and prognosis, 1217–1218
 ultrastructure of, 1217
- Solid parathyroid adenomas, 19
- Somatostatin analogue octreotide, 712
- Sonic Hedgehog (SHH)* gene underexpression in ameloblastomas, 1213
- SOT. *See* Squamous odontogenic tumor (SOT)
- South Asia, oral cancer incidence in, 287
- SPCC. *See* Spindlecell carcinomas (SPCC)
- Sphenoethmoidal, through sphenoethmoid junction, 674
- Sphenomaxillary, through sphenoid, 675
- Spheno-orbital through superior orbital fissure, 674
- Spindle cell carcinomas (SPCC), 146–151, 318–322, 1492
 clinical features, 147, 319
 diagnosis, 150
 etiology, 147
 immunohistochemistry, 149–150
 molecular genetic data, 150
 overviews, 146–147
 pathology, 147–149, 319–321
 treatment, 150–151
 treatment and prognosis, 321–322
- Spindle cell lesions, 35
- Spindle cell melanoma, 1509–1510
- Spindle cell rhabdomyosarcoma, 871–872
- Spindle cell sarcomas, 58
- Spindle epithelial tumor with thymus-like differentiation (SETTLE), 1412–1413
- Spindle-pleomorphic lipoma (SPL), 1728
- Spitz nevus
 clinical features, 1504
 differential diagnosis, 1506
 electron microscopy, 1506
 immunohistochemistry, 1506
 and melanocytic proliferation, 1340
 molecular genetics, 1506
 pathology, 1504–1506
 treatment and prognosis, 1506–1507
- Spitzoid melanoma, 1340
- Sporothrix, 1638
- Sporotrichosis, 1641–1642
- S-100 protein, 1286, 1500, 1729
- S-100 protein-positive cells, 683
- Squamous carcinoma, 21–22
- Squamous cell carcinoma (SCC), 588–589, 958, 1147
 metastasis determinants
 extracapsular spread, 1138–1140
 histologic prognostic factors, 1141–1142
 micrometastases, 1140–1141
 positive lymph nodes, 1140
- [Squamous cell carcinoma (SCC)]
[metastasis determinants]
 soft tissues, 1140
 stromal reactions, 1141
- Squamous cell carcinomas (SCC), 46–47, 61–62, 76, 1413–1414, 1476. *See also*
 Oral cancer
 clinical features, 1491
 differential diagnosis, 1494–1495
 of ear, 459–460
 eyelids, 1553
 of hypopharynx, 174–177
 clinical features, 175–177
 etiology, 175
 overviews, 174
 treatment, 177
 keratinizing. *See* Keratinizing squamous cell carcinomas (KSCC)
 of larynx, 137–145
 glottic carcinoma, 139–142
 laryngeal carcinoma, 144–145
 molecular genetic data, 145
 overviews, 137–139
 subglottic carcinoma, 142–143
 supraglottic carcinoma, 139
 transglottic carcinoma, 143
 maxillary sinuses, 374–376
 T staging, 375
 of middle ear, 465–466
 molecular genetics, 1494
 nasal cavity, 371–374
 of nasopharynx, 397
 nonkeratinizing. *See* Nonkeratinizing squamous cell carcinomas
 oral cavity, 292–301
 buccal mucosa, 294–295
 floor of mouth and oral tongue, 295–298
 gingiva and alveolar mucosa, 298–300
 hard palate, 300–301
 lip, 292–294
 oropharynx, 301–305
 oropharyngeal wall, 303
 palatine tonsils and base of tongue, 303–305
 retromolar trigone (RMT), 301–302
 soft palate and uvula, 302–303
 pathology, 1492–1494
 of trachea, 178
 glottic carcinoma, 139–142
 laryngeal carcinoma, 144–145
 molecular genetic data, 145
 overviews, 137–139
 subglottic carcinoma, 142–143
 supraglottic carcinoma, 139
 transglottic carcinoma, 143
 treatment and prognosis, 1495
 of upper aerodigestive tract, 1459
 variants, 1492–1494
- Squamous eddies, 1479
- Squamous intraepithelial neoplasia
 classification, 270
- Squamous metaplasia, nasal polyps with, 368
- Squamous odontogenic hamartoid lesions (SOHL), 1229
- Squamous odontogenic tumor (SOT)
 etiology and pathogenesis, 1228–1229
 histochemical markers for, 1229
 hyperplastic islands, 1229
 molecular-genetic data, 1230
 prevalence and incidence, 1228
 radiograms of, 1228
 treatment and prognosis, 1230
- Stafne cyst, 962
- Stapedial footplate, otosclerosis of, 445
- Staphylococcus aureus*, 50, 953, 1609
- Sternomastoid tumor. *See* Fibromatosis colli
- Steroid therapy, 254
- Stevens-Johnson syndrome (SJS), 258
- Stomal recurrence, 144–145
- Storiform pleomorphic malignant fibrous histiocytoma, 886, 888
- Stratum fibrosum externum, 672
- Stratum fibrosum internum, 670
- Stratum nervosum, 670
- Streptococcus*, 261
- Streptococcus pneumoniae*, 345, 429, 1392, 1609
- Stromal atypia, nasal polyps, 350
- Stromal dystrophies, 1570–1571
- Stucco keratosis. *See* Seborrheic keratoses (SKs)
- Sturge-Weber syndrome, 1523
- Subacute cutaneous lupus erythematosus (SCLE), 252–253
- Subacute granulomatous thyroiditis, 4
- Subacute necrotizing sialadenitis, 493
- Subacute sclerosing panencephalitis (SSPE), 1685
- Subacute thyroiditis, 1392
- Subcutaneous lymphoid infiltrate
 diagnosis, of hematomalymphoid lesions of skin, 1115
- Subcutaneous panniculitis-like T-cell lymphoma, 1071
- Subglottic carcinoma, 142–143
- Subglottic stenosis, 114
- Sulfodiazine, 1689
- Sulfonamides, 260
- Superficial extending carcinoma (SEC), 136–137
- Superficial lymph nodes
 lateral, 1135
 medial, 1135
- Supernumerary parathyroid glands, 1429, 1430
- Suppurative granulomas, 1012
- Suppurative lymphadenitis, 50
- Suprabasal bullae formation, 244
- Supraclavicular lymph node metastases, 48–49
- Supraglottic carcinoma, 139
- Surgical margins, 97–100
- Surgical resection, of cancer, 98
- Sympathetic ophthalmia, 1583–1586
- Synaptophysin, 67
- Syndecan-1 (SDC-1) for Wnt induced carcinogenesis, 1213
- Syndrome-associated osteosarcoma, 974
- Synovectomy, 956
- Synovial chondromatosis
 pathologic features, 955–956
 radiologic features, 955
- Synovial chondromatosis of temporomandibular joint, 435–436
- Synovial cysts, 957
- Synovial sarcomas, 56–57, 897–899, 1360
 biphasic, 897
 monophasic, 897
- Syphilis
 congenital, 1615, 1616
 differential diagnosis, 1617
 epidemiology and historical perspective, 1612–1613
 head and neck manifestations, 1613–1614
 oral manifestations, 1613
 otosyphilis, 1614
 primary, 1615–1616
 secondary, 1616
 serologic identification, 1617
 and spirochetes, 1616–1617
 tertiary, 1614–1615, 1616
 treatment, 1617
- Syphilitic (luetic) lymphadenitis, 1012
- Syringocystadenoma papilliferum, ceruminal gland, 447–448

- Syngomas, 1342
 clinical features, 1485–1486
 differential diagnosis, 1486–1487
 electron microscopic studies, 1486
 immunohistochemistry, 1486
 molecular genetics, 1486
 pathology, 1486
 treatment and prognosis, 1487
- Systemic lupus erythematosus (SLE), 252
- Tachyzoites, 1688
- Tamoxifen, 1390
- Tangier disease (TD), 1730
- Tapered stroma, of the ciliary body, 1587
- Tartrateresistant acid phosphatase (TRAP), 557
- TC. *See* Typical carcinoid (TC)
- T-cell intracellular antigen (TIA)-1, 43
- T-cells, 39, 257, 260
 lymphoblastic leukemia/lymphoma, 1060
 receptor gene, 40
 rich B-cell lymphomas, 660
- Teflon granulomas, 113–114, 1393
- Teflon injections, 976
- Teflonoma. *See* Teflon granuloma
- Telangiectasias, 1533
- Telangiectatic osteosarcoma, 973–974
- Temporal bone
 benign neoplasms of, 449–456
 endolymphatic sac papillary tumor, 457–458
 metastases, 1157
 metastatic tumors, 467
 neoplastic lesions of, 446–467
 benign neoplasms, 447–456
 endolymphatic sac papillary tumor, 457–458
 malignant neoplasms, 459–467
 nonneoplastic lesions, 425–432
- Temporomandibular joint (TMJ), 953
 synovial chondromatosis of, 435–436
- Tenascin
 and calcifying odontogenic cyst (COC), 1265
 CEOT, 1234
 and DESAM, 1220
 solid/multicystic ameloblastoma–central, 1208
- Teratocarcinoma, 1366
- Teratoma, 1414
- Terminal deoxynucleotidyl transferase
 biotin-dUTP-nick-end labeling (TUNEL) for apoptosis detection, 1212
- Tertiary hyperparathyroidism
 clinical presentation, 1442
 definition, 1442
 epidemiology, 1442
 imaging studies, 1442–1443
 preoperative localization, 1442–1443
 selective venous sampling, 1443
 treatment and prognosis, 1456
- Tetracycline, 263
- TGF- β . *See* Transforming growth factor beta (TGF- β) role in ameloblastomas
- Thalidomide, 1693
- Thiabendazole, 1690
- Thiazide diuretics, 1438
- Thiocyanate antithyroid drugs, 1386
- Thorotrast granulomas
 background, 1722–1723
 clinical features, 1723
 pathology, 1723–1724
 treatment and prognosis, 1724
- Thorotrast injection, 1723–1724
- Thorotrast-related hepatic malignancies, 1724
- Thorotrast-related neoplasms, 1723
- Thymidine phosphorylase (PD-ECGF/TP)
 expression and stroma of ameloblastomas, 1211
- Thymomas, 1724
- Thyroglobulin, 1386
- Thyroglossal duct cyst (TGDC), 16, 1351–1352, 1387
- Thyroid, hematolymphoid lesions of, 1100–1103
 diagnostic considerations, 1102–1103
 neoplasms, 1100–1101
 reactive/inflammatory, 1101–1102
- Thyroid carcinoma, 47
- Thyroid cyst fluid, 16
- Thyroidectomy, 13, 15, 1429, 1432
- Thyroid gland, 103–104
 adequacy criteria, 2–3
 clear cell lesions, 16–17
 clinical implications of, 17
 cystic lesions, 15–16
 developmental and hereditary abnormalities
 aplasia and hypoplasia, 1387
 ectopic thyroid tissue, 1387
 hereditary abnormalities, 1387
 parasitic nodule, 1387
 thyroglossal duct cyst, 1387
- diagnostic accuracy, 2
- diagnostic categories, 1–2
- disorders
 autoimmune thyroid diseases, 1390
 crystals, 1393
 goiters, 1390–1391
 hypothyroidism, 1392–1393
 infections and granulomatous diseases, 1391–1392
 levothyroxine therapy, 1390
 metabolic diseases, 1392
 pigment deposition, 1393
 teflon, 1393
- drugs effects of, 1386
- embryology and development, 1385–1386
- follicular lesions, 6–9
- invasion, 145
- malignant neoplasms, 9–15
 metastatic malignancies, 17–18
 nonneoplastic disease, 3–6
 oncocyctic neoplasms, 9
 overviews, 1
- physiology
 thyroid-stimulating hormone (TSH), 1386
 thyroxine (T4) and triiodothyronine (T3), hormones, 1386
- radiation changes in, 1386–1387
- thyroid parenchyma, 1365
- thyroid transcription factor-I (TTF-1), 1385
- thyrotropin receptor gene, genetic alterations of, 1387
- tumors
 anaplastic carcinoma, 1407–1409
 carcinoma showing thymus-like differentiation, 1413
 of C Cells, 1409–1412
 follicular thyroid tumors, 1402–1404
 hurthle cell tumors, 1404–1406
 hyalinizing trabecular tumor, 1400–1402
 langerhans cell histiocytosis, 1415
 mesenchymal tumors, 1415–1416
 mucoepidermoid carcinoma, 1412
 papillary thyroid carcinoma (PTC), 1393–1400
 poorly differentiated carcinomas, 1406–1407
- [Thyroid gland]
 [tumors]
 primary lymphomas and plasmacytomas, 1414–1415
 sclerosing mucoepidermoid carcinoma with eosinophilia, 1412
 sinus histiocytosis with massive lymphadenopathy, 1415
 smooth muscle tumors, 1416
 solitary fibrous tumor, 1415
 spindle epithelial tumor with thymus-like differentiation, 1412–1413
 squamous cell carcinoma, 1413–1414
 teratoma, 1414
- Thyroiditis, 3–4
- Thyroid nodule, 1
- Thyroid parangliomas (TPG), 725
- Thyroid transcription factor (TTF)-1, 1503
- Thyroid transcription factor-1 (TTF-1), 15
- Ticarcillinclavulanate, 1611
- Tissue alterations, in dysplasia, 267
- Tissue culture, in cranial fasciitis, 966
- Tissue eosinophilia, 658
- TLA-1. *See* T-cell intracellular antigen (TIA)-1
- T- lymphocytes, 952, 953
- TMJ. *See* Temporomandibular joint (TMJ)
- TNF-related apoptosis-related ligand (TRAIL) 1 and 2, role in ameloblastomas, 1212
- TNM classification scheme, 1507–1508
- Tobramycin, 1612
- Tonsillar cysts, 117
- Tonsillar hyperplasia, 222–225, 1610
- Tonsillectomy, 1610
- Tonsillitis, 222–225, 1610
 clinical features, 223
 overviews, 222–223
 pathology, 223–224
 treatment, 224–225
- Tophaceous gout, 442–443
- Tophus, 953
- Topical 5-aminolevulinic acid-mediated photodynamic therapy, 1678
- Torg syndrome, 1344
- Torus mandibularis, 967
- Torus palatinus, 967
- Toxic multinodular goiter, 1391
- Toxoplasma gondii*, 50
- Toxoplasmic lymphadenitis, 1012–1013
- Toxoplasmosis, 50–51
 clinical course, 1687–1688
 epidemiology, 1687
 histopathology, 1688
 IHC, PCR, and serology, 1688–1689
 treatment, 1689
- TPG. *See* Thyroid parangliomas (TPG)
- TP53 gene family in ameloblastomas, 1211
- TPO. *See* Tracheopathia osteochondroplastica (TPO)
- Trachea, hematolymphoid lesions of, 1100
- Tracheopathia osteochondroplastica (TPO), 114–115
- TRAIL/Apo2L. *See* Tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL/Apo2L) expressions and ameloblastomas
- Transcription factor deficiency, 1387
- Transethmoidal, through cribriform plate, 674
- Transforming growth factor beta (TGF- β) role in ameloblastomas, 1211
- Transglottic carcinoma, 143
- Transillumination, of the eye, 1583
- Transsphenoidal, through sphenoid, 675
- TRAP. *See* Tartrateresistant acid phosphatase (TRAP)

- Traumatic neuroma
clinical features, 676–677
diagnosis, 677
histopathology, 677
immunohistochemistry, 677
macroscopy, 677
overview, 676
treatment, 677–678
ultrastructure, 677
- Traumatic retinal detachment, 1585
- Treponema pallidum*, 1012
- Trichilemmal carcinoma (TLC), 1479
clinical features, 1501
differential diagnosis, 1502
immunohistochemistry, 1502
pathology, 1501–1502
treatment and prognosis, 1502
- Trichilemmal cyst. *See* Pilar cysts (PCs)
- Trichilemmal keratinization, 1477
- Trichilemmomas (TL)
clinical features, 1481
differential diagnosis, 1482
imaging studies, 1481
immunohistochemistry, 1481–1482
molecular genetics, 1482
pathology, 1481
treatment and prognosis, 1482
- Trichinella*, 1689
- Trichinosis
clinical course, 1689
etiology, 1689
histopathology, 1689–1690
serology, 1690
treatment, 1690
- Trichloroacetic acid treatment, 1487
- Trimethoprim sulfamethoxazole, 1691
- Trimethoprim-sulfamethoxazole (TS), 655
- Trousseau's sign, 1460
- Trypanosome, 1654
- TS. *See* Trimethoprim-sulfamethoxazole
- T-SPOT-TB, 1623
- T staging of squamous cell carcinomas
external auditory canal, 462
in maxillary sinus, 375
- TTF-1. *See* Thyroid transcription factor-I (TTF-1)
- Tuberculin skin test, 1623
- Tuberculosis and thyroiditis, 1392
- Tuberous sclerosis, 1348
- Tumefactive fibroinflammatory pseudotumor, 1367
- Tumoral calcinosis, 954–955
- Tumor necrosis factor α (TNF- α), 655, 958
- Tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL/Apo2L) expressions and ameloblastomas, 1212
- Tumor-node-metastasis (TNM) staging, 1495
malignant melanomas, 394
for oral cavity cancer, 291
for oropharyngeal cancer, 292
of squamous cell carcinomas in external auditory canal, 462
- Tumors
of parapharyngeal space
anatomy, 1721–1722
clinical features, 1722
histology, 1722
pathology, 1722
treatment and prognosis, 1722
of parathyroid glands
clinical features, 1461–1462
differential diagnosis, 1462
pathologic features, 1462
treatment and prognosis, 1462
ploidy, 145
thyroid glands. *See* Thyroid gland, tumors
- Tumors, of trachea, 177–178
adenoid cystic carcinoma, 178
anatomy, 177–178
overviews, 177
squamous cell carcinoma, 178
- Tumors, salivary gland
age distribution, 506
cigarette smoking and, 506–507
classifications, 511
epidemiology, 505–506
fine-needle aspiration cytology for, 508–509
frozen section diagnosis, 509
genetics, 510–511
imaging procedures of, 507–508
occupation and, 506
radiation and, 506
sex ratio, 506
site, 506
viruses and, 506
- TUNEL. *See* Terminal deoxynucleotidyl transferase biotin-dUTP-nick-end labeling (TUNEL) for apoptosis detection
- Turner syndrome, 1357, 1523
- T1-weighted images, 980
- T2-weighted images, 980
- Tympanic cavity, 424
- Tympanic paraganglioma, 721
- Tympanosclerosis, 429–430
- Typical carcinoid (TC), 162–164
clinical features, 162–163
diagnosis, 164
electron microscopy, 164
immunohistochemistry, 163–164
pathology, 163
treatment, 164
- Tyr165Cys, 1487
- Tzanck cells, 245, 262
- UDCs. *See* Undifferentiated carcinomas
- Ulceration, 1478
- Ultrasonography, 78
- Ultrasound (US), 1, 953
- Ultraviolet light (UV), 252
oral cancer, 288
- Ultraviolet (UV) B radiation, 1491
- UNAM. *See* Unicystic ameloblastoma (UNAM)
- Undifferentiated carcinomas (UDCs), 1141
nonkeratinizing, 308–309
of salivary glands, 589
- Undifferentiated nasopharyngeal carcinomas (UNPC), 397
versus SNUC, 380
- Unencapsulated parathyroid cells, 1431
- Unicystic ameloblastoma (UNAM)
AgNOR activity, 1224
differential diagnosis, 1224
etiology of, 1222–1223
histological variants of, 1223
immunohistochemistry, 1223–1224
molecular-genetic data, 1224
multilocularity and, 1222
PCNA and Ki-67 expression, 1224
prevalence and incidence, 1221–1222
treatment and prognosis, 1224–1225
type 1 (intralingual) and type 2 (intraluminar), 1225
- United States, oral cancer incidence in, 286
- UNPC. *See* Undifferentiated nasopharyngeal carcinomas (UNPC)
- Upper aerodigestive tract
nasal cavity and nasopharynx, 1343–1351
oral cavity and oropharynx, 1343–1348
- Urbach-Wiethe syndrome. *See* Lipoid proteinosis
- Uremia, 252
- US. *See* Ultrasound (US)
- UV. *See* Ultraviolet light (UV)
- Uveal tract
anatomy, 1586–1587
clinical features, 1587–1588
pathology, 1588–1591
specimen handling, 1587–1591
- UV light-induced SCCs, 1494
- Uvula, squamous cell carcinomas, 302–303
- Vagal paragangliomas (VPG), 722–723
- Varicella Zoster virus (VZV), 1661
- Vascular endothelial growth factor (VEGF) role in ameloblastomas, 1214
- Vascular malformations
clinical features, 1522
differential diagnosis, 1522–1524
electron microscopy, 1522
genetics, 1522
imaging studies, 1522
immunohistochemistry, 1522
pathology, 1522
treatment and prognosis, 1524
- Vascular neoplasms, in children, 1355
- Vascular proliferations
angiolymphoid hyperplasia with eosinophilia (ALHE), 1528–1529
infantile hemangioma (IH), 1524–1526
kaposiform hemangioendothelioma, 1526–1528
kaposi sarcoma, 1530–1532
syndromes associated with, 1523
vascular malformations, 1521–1524
vascular tumors, 1524
- Vascular transformation of sinuses, 1005–1006
- Vasomotor rhinosinusitis, 345–346
- VCA. *See* Viral capsid antigen (VCA)
- VCNP. *See* Vocal cord nodule and polyp (VCNP)
- VEGF. *See* Vascular endothelial growth factor (VEGF)
- Venous drainage, of parathyroids, 1430
- Venous malformations, 1522
- Vernal conjunctivitis, 72
- Verruca vulgaris, 214–215, 1476
- Verruca vulgaris of larynx (VVL), 124–125
- Verruciform xanthoma, 216–217
- Verrucous carcinomas, 151–153, 314–316, 1492
clinical features, 151, 314
diagnosis, 153
differential diagnosis, 315–316
etiology, 151–152
molecular-genetic data, 152–153
overviews, 151
pathology, 152, 315
treatment, 153
treatment and prognosis, 316
and verrucous hyperplasia, 1677–1678
- Verrucous hyperplasia (VH), 1678
- Versican and calcifying odontogenic cyst (COC), 1265
- Vesiculoerosive lesions, 243
- Vimentin antibodies
AFOD, 1251
and AMF, 1244
AOT, 1238
and (ODOMYX), 1286
- Viral capsid antigen (VCA), 1150
- Viral diseases, 72
- Vitamin C, 1691
- Vitamin D analogues, 1456

- Vitamin D receptor (VDR), 1435
 Vitrectomy, 70
 Vocal cord nodule and polyp (VCNP), 109–111
 clinical features, 109
 diagnosis, 111
 etiology, 109
 overviews, 109
 pathology, 109–110
 treatment, 111
 Vogt-Koyanagi-Harada syndrome (VKH), 1584
 Von Hippel-Lindau (VHL) syndrome, 457
 Vossius ring, 1586
 VPG. *See* Vagal paragangliomas (VPG)
 VVL. *See* Verruca vulgaris of larynx (VVL)
- Waldeyer's ring, 1147
 normal lymphoid tissues of, 1001
 Warthin-Starry stain, 64
 Warthin's tumor, 505
 cigarette smoking and, 507
 clinical features, 526
 differential diagnosis, 529–530
 electron microscopy, 529
 etiology, 526–527
 imaging, 526
 immunohistochemistry, 529
 molecular-genetic data, 529
 overview, 526
 pathology, 527–529
 treatment, 530
 Warthin tumor, 22, 30–31
 Water-clear cells, 1448, 1454
- WDLS. *See* Well-differentiated liposarcoma (WDLS)
 Weathering nodule of the ear (WNE)
 clinical features, 1535
 differential diagnosis, 1536
 immunohistochemistry, 1536
 pathology, 1535
 treatment and prognosis, 1536
 Wegener's granulomatosis (WG), 73, 443–444, 961, 1392, 1610
 clinical features, 650–652
 criteria for diagnosis, 652
 ELK classification, 654
 etiology, 649–650
 limited form of (LWG), 653–654
 nasal cavity, 1083
 pathology, 652–654
 treatment and prospect, 654–655
 Well-differentiated liposarcoma (WDLS), 862
 "Western" sinonasal lymphomas, 1670
 Wet keratin, 715
 WG. *See* Wegener's granulomatosis
 Whipple's disease, 73, 1691
 White sponge nevus
 clinical features, 201–202
 diagnosis, 203
 molecular and genetic data, 203
 pathology, 202
 treatment, 203
 WHO. *See* World Health Organization (WHO)
 Wickham's striae, 254
 Winkler disease. *See* Chondrodermatitis nodularis chronicus helici (CNCH)
- Wiskott-Aldrich syndrome (WAS), 1667
 Wnt signaling pathway in ameloblastomas, 1213
 World Health Organization (WHO), 37, 43, 269
 classification
 ossifying fibroma, 970
 osteosarcoma, 972
 dysplasia classification by, 269–270
 histological classification of odontogenic tumors, 1202
- Xanthelasma, 1557
 Xanthogranuloma, juvenile, 1085
 X chromosome-linked IAP (XIAP), and odontogenic epithelial cells, 1212
 Xeroderma pigmentosa, 1341
 Xeroderma pigmentosum, 76
 XIAP. *See* X chromosome-linked IAP (XIAP) and odontogenic epithelial cells
 X-linked idiopathic hypoparathyroidism, 1460
 X-linked lymphoproliferative syndrome, 1667
- Yolk sac carcinoma, 1365
- ZEBRA, 1665
 Ziehl-Neelsen stain, 1623
 Zimmerman tumor. *See* Phakomatous choristoma
 Zygomycetes, 1638

about the book...

Surgical Pathology of the Head and Neck, Third Edition is a complete stand-alone reference covering all aspects of head and neck pathology. Providing an interdisciplinary approach to the diagnosis, treatment, and management of head and neck diseases, this source promotes clear communication between pathologists and surgeons. This is the reference of choice for a variety of clinicians, including: oral and general pathologists; oral and maxillofacial, plastic, reconstructive, head and neck, orthopedic, and general surgeons; otolaryngologists; radiologists; and dentists.

Topics covered include:

- incidence
- etiology
- clinical presentation
- pathology
- differential diagnosis
- prognosis for each disorder

With an improved format and design as well as an easy-to-use, quick reference index, the updated and expanded ***Third Edition*** contains more than 1,400 images—200 more full-color images than in previous editions—for optimal illustrations of head and neck lesions.

about the editor...

LEON BARNES is Professor of Pathology and Otolaryngology, Chief of the Division of Head and Neck–Endocrine Pathology and Director of the Head and Neck–Endocrine Pathology Fellowship Program at the University of Pittsburgh Medical Center, and Professor of Oral and Maxillofacial Pathology at the University of Pittsburgh School of Dental Medicine. Dr. Barnes obtained his M.D. degree from the University of Arkansas, Little Rock, Arkansas. He is a founding member of the North American Society of Head and Neck Pathology and has been a frequent honoree on the “Best Doctors in America” list for head and neck pathology. He has contributed numerous peer-reviewed publications, is a co-editor of the most recent World Health Organization “Blue Book” on the Pathology and Genetics of Head and Neck Tumors, and is the editor of the two previous editions of Informa Healthcare’s ***Surgical Pathology of the Head and Neck***.

Printed in India

informa
healthcare
www.informahealthcare.com

52 Vanderbilt Avenue
New York, NY 10017
Telephone House
69-77 Paul Street
London EC2A 4LQ, UK

H9163

